#25

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	**Yamanouchi Pharmaceutical Co., Ltd.**	
		DATE: December 20, 2004
U.S. PATENT NO.:	**6,017,927**	
ISSUED:	**January 25, 2000**	

Application for Extension of Patent Term Pursuant to 35 U.S.C. § 156

Mail Stop: Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Yamanouchi Pharmaceutical Co., Ltd ("Yamanouchi" or "the Applicant"), Assignee of the above-identified patent, hereby petitions for extension of U.S. Patent No. 6,017,927 pursuant to 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and states in part thereof as follows:

(1) **A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS.**

The United States Food and Drug Administration ("FDA") has approved a New Drug Application ("NDA") (NDA # 21-518) for a human drug product, i.e., VESIcare® (solifenacin succinate) film-coated tablet (hereinafter "Product"), which is effective for relief of symptoms of urinary frequency, urinary urgency or urinary incontinence associated with overactive bladder. The chemical name of solifenacin is:

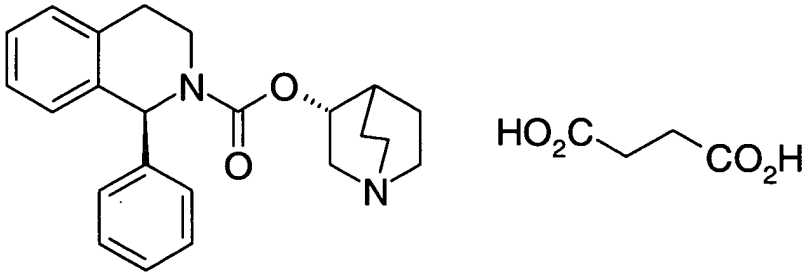
(+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate

(1*S*)-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1*H*)-isoquinolinecarboxylate; or

(3*R*)-3-quinuclidinyl (1*S*)-1-phenyl-1,2,3,4-tetrahydro-2- isoquinolinecarboxylate; or

(3*R*)-1-azabicyclo[2.2.2]oct-3yl (1*S*)-1-phenyl-3,4-dihydroisoqunoline -2(1*H*)-carboxylate.

with a molecular formula of $C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$, a molecular weight of 480.56, and a structural fomula of:



(2) **A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED.**

The regulatory review occurred under § 505 of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 355.

(3) **AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED.**

FDA approved NDA #21-518 for VESIcare® (solifenacin succinate) film-coated tablet for commercial marketing under § 505(b) of the FDC Act on November 19, 2004.

(4) **IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FDC ACT, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT, OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE**

INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The only active ingredient in the Product (which is a human drug) is solifenacin succinate. FDA has not previously approved solifenacin succinate for commercial marketing or use under the FDC Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) **A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO 37 C.F.R. § 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED.**

FDA approved the Product on November 19, 2004. The last day within the sixty-day period permitted for submission of an application for extension of a patent is January 18, 2005. This application is being submitted before January 18, 2005.

(6) **A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION.**

The patent for which an extension is being sought is U.S. Patent No. 6,017,927, which issued on January 25, 2000 to Makoto Takeuchi, Ryo Naito, Masahiko Hayakawa, Yoshinori Okamoto, Yasuhiro Yonetoku, Ken Ikeda, and Yasuo Isomura, and which is assigned to Yamanouchi Pharmaceutical Co., Ltd. The assignment was recorded in the USPTO on August 28, 1997, at reel 008827, frame 0376. A copy of the assignment of the patent to Yamanouchi is attached hereto as Attachment 1. U.S. Patent No. 6,017,927 is scheduled to expire on December 27, 2015.

(7) **A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS.**

A copy of U.S. Patent No. 6,017,927 is attached hereto as Attachment 2.

(8) **A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT.**

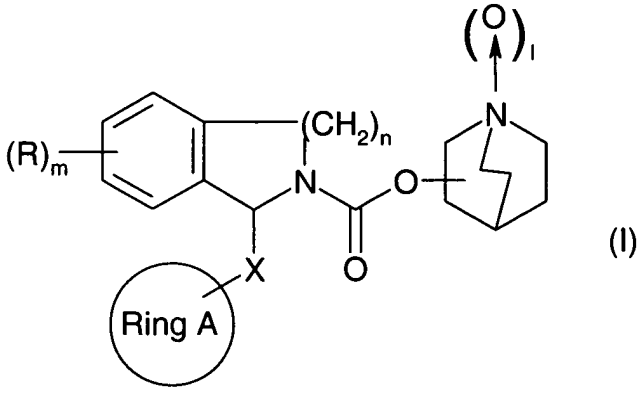
There are no disclaimers or reexamination certificates. Certificates of correction and a maintenance fee payment receipt are attached hereto as Attachments 3A, 3B, and 3C.

(9) **A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT .**

U.S. Patent No. 6,017,927 claims the Product and also claims a composition of matter comprising the drug product.

Claim 1

A quinuclidine derivative represented by the following formula (I):



(I)

where the symbols in the formula have the following meanings: Ring A:

(1) an aryl group having 6 to 14 carbon atoms

(3) a cycloalkyl group having 3 to 8 carbon atoms

(4) a cycloalkenyl group having 3to 8 carbon atoms;

wherein groups (1) to (5) above may be unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group,

a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower aklylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group, and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxyl group, an amino group or mono- or di-lower alkylamino group

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsufinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1;

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2,

a salt thereof, an N-oxide thereof, or a quaternary ammonium salt thereof.

Claim 2

The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to claim 1, wherein R represents a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and the ring A represents an aryl group having 6 to 14 carbon atoms, a cycloalkyl group having 3 to 8 carbon atoms or a cycloalkenyl group having 3 to 8 carbon atoms, in which said ring may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxyl group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group.

Claim 3

The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to claim 2, wherein m is 0, and the ring A represents an aryl group, a cycloalkyl group or a cycloalkenyl group which may be substituted by a halogen atom, a

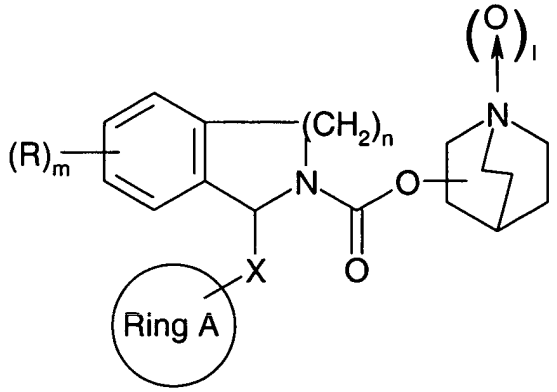
lower alkyl group, a hydroxyl group or a lower alkoxy group.

Claim 4
The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to claim 3, wherein the ring A represents a phenyl group which may be substituted by a halogen atom or a lower alkyl group, or cycloalkyl group.

Claim 5
The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to any one of claims 2 to 4, wherein X represents a single bond.

Claim 6
A quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to any one of claim 1, which is selected from the group consisting of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate, and 3-quinuclidinyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate.

Claim 7
A pharmaceutical composition which comprises a quinuclidine derivative represented by the following formula (I):



(I)

where the symbols in the formula have the following meanings: Ring A:

(1) an aryl group having 6 to 14 carbon atoms

(3) a cycloalkyl group having 3 to 8 carbon atoms

(4) a cycloalkenyl group having 3 to 8 carbon atoms;

wherein groups (1) to (5) above may be unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxul group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower aklylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxyl group, an amino group or mono- or di-lower alkylamino group

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsufinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1;

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2, or
a salt thereof, an N-oxide thereof, or a quaternary ammonium salt thereof, and a pharmaceutically acceptable carrier.

The applicable patent claims which read on the Product are Claims 1,2,3,4,5,6 and 7.

Claim 1 reads on the Product because the Product is the succinate of the (+) optically active isomer of (1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate which is a compound of the formula of Claim 1 wherein Ring A is a phenyl group, which is (1) an aryl group having 6 to 14 carbon atoms, X is a single bond, l is 0, m is 0, n is 2 and R does not exist, because m is 0.

Claim 2 reads on the Product because the Product is the succinate of the (+) optically active isomer of (1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate which is a compound of Claim 1 wherein Ring A is a phenyl group, which is an aryl group having 6 to 14 carbon atoms and R does not exist, because m is 0.

Claim 3 reads on the Product because the Product is the succinate of the (+) optically active isomer of (1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate which is a compound of Claim 2 wherein m is 0, Ring A is a phenyl group, which is an aryl group.

Claim 4 reads on the Product because the Product is the succinate of the (+) optically active isomer of (1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate which is a compound of Claim 3 wherein Ring A is a phenyl group.

Claim 5 reads on the Product because the Product is the succinate of the (+) optically active isomer of (1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate which is a compound of any one of Claims 2 to 4 wherein X is a single bond.

Claim 6 reads on the Product because the Product is the succinate of the (+) optically active isomer of the compound specifically named in Claim 6.

Claim 7 reads on the Product because the Product is a pharmaceutical composition which comprises the succinate of the (+) optically active isomer of (1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate which is a compound of the formula of Claim 7 wherein Ring A is a phenyl group, which is (1) an aryl group having 6 to 14 carbon atoms, X is a single bond, l is 0, m is 0, n is 2 and R does not exist, because m is 0.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD.

The relevant dates and information pursuant to 35 U.S.C. § 156(g) needed to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

The Investigational New Drug Application ("IND") for the Product became effective on May 5, 1999 (IND #58,135).

New Drug Application ("NDA") #21-518 was submitted to FDA on December 19, 2002.

FDA approved NDA #21-518 on November 19, 2004.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES.

DATE TO FDA	DESCRIPTION
02 Apr. 1999	Initial IND Application
17 Jun. 1999	Protocol Amendment Information Amendment: Pharm/Tox
09 Dec. 1999	Information Amendment: Clinical
03 March 2000	Protocol Amendment
12 Apr. 1999	Information Amendment: Pharm/Tox; Clinical Protocol Amendment
30 June 2000	Annual Report
01 Sept. 2000	Protocol Amendment
14 Sept. 2000	Information Amendments: Chemistry, Pharm/Tox, Clinical
18 Oct. 2000	Protocol Amendment: Updated Investigators Brochure
16 Nov. 2000	Protocol Amendment
05 Dec. 2000	Information Amendment
21 Dec. 2000	Information Amendment: Toxicology, Chemistry
01 Feb. 2001	Protocol Amendment
16 Feb. 2001	Request for Comment
21 February 2001	Information Amendment
27 February 2001	Protocol Amendment
21 March 2001	Protocol Amendment
09 April 2001	Protocol Amendment
03 May 2001	Protocol Amendment
30 May 2001	Protocol Amendment
01 June 2001	Information Amendment
18 June 2001	Protocol Amendment
29 June 2001	Annual Report
05 July 2001	Information Amendments
13 July 2001	Information Amendment
17 July 2001	Protocol Amendment
14 August 2001	Protocol Amendment
17 August 2001	Protocol Amendment
19 September 2001	Protocol Amendment
28 September 2001	Protocol Amendment
19 October 2001	Protocol Amendments
01 November 2001	Protocol Amendments

DATE TO FDA	DESCRIPTION
09 November 2001	Other Amendment: Statistical Analysis Plan
06 December 2001	Protocol Amendment
21 January 2002	Protocol Amendment
25 January 2002	Other Amendment
29 January 2002	Other Amendment
13 February 2002	Protocol Amendment
14 February 2002	Other Amendment
15 February 2002	Other Amendment
18 February 2002	Other Amendment
26 February 2002	Other Amendment
06 March 2002	Other Amendment
14 March 2002	Information Amendment: Pharmacology/Toxicology, Clinical
22 March 2002	Other Amendment: Investigator's Brochure
11 June 2002	Protocol Amendment
01 July 2002	Annual Report
06 August 2002	Protocol Amendment
27 August 2002	Other Amendment
25 September 2002	Other Amendment
30 September 2002	Other Amendment
19 December 2002	New Drug Application #21-518
24 January 2003	Protocol Amendment
19 February 2003	Protocol Amendments
27 February 2003	Information Amendment
26 March 2003	NDA Field Copy Submission
03 April 2003	Information Amendment
11 April 2003	Information Amendment
25 April 2003	4-Month safety update
06 May 2003	Protocol Amendment
08 May 2003	CMC Amendment
13 May 2003	Information Amendment
13 June 2003	CMC Amendment
16 June 2003	Clinical Amendment
26 June 2003	Information Amendment
15 July 2003	Information Amendment
28 July 2003	Information Amendment
25 August 2003	Information Amendment
29 August 2003	Information Amendment
11 September 2003	Information Amendment
19 September 2003	Draft Labeling
22 September 2003	Information Amendment

DATE TO FDA	DESCRIPTION
26 September 2003	Response to FDA Request for Information
03 October 2003	Response to FDA Request for Information
09 October 2003	Response to FDA Request for Information
15 October 2003	Response to FDA Request for Information
16 October 2003	Response to FDA Request for Information
20 October 2003	Response to FDA Approvable Letter
11 November 2003	Protocol Amendment
09 December 2003	Information Amendment
24 March 2004	Response to FDA Request for Information
18 May 2004	Complete Response to Approvable Letter of October 17, 2003
18 June 2004	Clinical Amendment
17 September 2004	Information Amendment
24 September 2004	Information Amendment
30 September 2004	Information Amendment
29 October 2004	Response to FDA Comments
01 November 2004	Response to FDA Comments
08 November 2004	Response to FDA Comments
17 November 2004	Response to FDA Comments
18 November 2004	Submission of Final Draft Labeling

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED.

It is the opinion of Yamanouchi that U.S. Patent No. 6,017,927 is eligible for extension, because: (a) the patent claims the Product or a method of using the Product; (b) the term of the patent has never been extended; (c) this application is submitted in compliance with all requirements of 37 C.F.R. § 1.740; (d) the Product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use; (e) Yamanouchi has received permission from FDA for commercial marketing or use of the Product and the permission for the commercial marketing or use of the Product is the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred; (f) this Application for Extension is submitted within the sixty-day period after the Product first received permission for commercial marketing and use; (g) the term of the patent has not expired before submission of this Application for Extension; and (h) no other patent term has been extended for the same regulatory review period for the Product.

Yamanouchi further believes that U.S. Patent No. 6,017,927 is entitled to an extension of 2 years 327 days as determined by the following:

(i) Number of days of the testing phase subsequent to issuance of the patent (January 25, 2000 to December 18, 2002) is 1059 days. The IND for the Product became effective on May 5, 1999, but U.S. Patent No. 6,017,927 issued on January 25, 2000.

(ii) One half of the testing phase is 529 days.

(iii) Number of days in the approval phase (December 19, 2002 to November 19, 2004 is 702 days.

(iv) The sum of (ii) and (iii) is 1,231 days.

(v) The patent was issued after the enactment date of 35 U.S.C. § 156, September 24, 1984, and the IND and NDA for the Product were filed subsequent to that date. Therefore, the term of the patent may only be extended for up to five years under 35 U.S.C. § 156(g)(1)(B) and 35 U.S.C. § 156(g)(6)(A).

(vi) The patent term extension is also subject, under 35 USC 156(c)(3), to the fourteen year limitation as to the net effective life of the patent after the NDA approval. This limitation dictates that the subject patent cannot be extended beyond November 19, 2018. Adding 1,231 days to the term of the

patent remaining after the date of NDA approval of the Product exceeds fourteen years.

(vii) In light of the above, the extended expiration date of the subject patent is believed to be November 19, 2018, namely 2 years and 327 days after the date of the current patent term expiration (fourteen years after the date of NDA approval).

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

Yamanouchi acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to any determinations to be made relative to this Application for Extension.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION.

Please charge deposit account number 194880 in the amount of $1,120.00.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED.

Inquiries and correspondence relating to this Application for Extension should be directed to:

Susan J. Mack
Sughrue Mion, PLLC
2100 Pennsylvania Ave., N.W.
Washington, D.C. 20037-3213
T: 202-293-7060
F: 202-293-7860
Email: smack@sughrue.com

(16) FOUR ADDITIONAL COPIES OF THE APPLICATION PAPERS

Four additional copies of the application are attached hereto as Attachment 4.

By: Susan J Mack

Susan J. Mack
Registration Number 30,951

Date: December 20, 2004

ATTACHMENT 1

Assignment

Whereas, I/We, Makoto TAKEUCHI, Ryo NAITO, Masahiko HAYAKAWA, Yoshinori OKAMOTO, Yasuhiro YONETOKU and Yasuo ISOMURA of Ibaraki, Japan and Ken IKEDA of Chiba, Japan

hereinafter called assignor(s), have invented certain improvements in

NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

and executed an application for Letters Patent of the United States of America therefor on July 28, 1997; and

Whereas, YAMANOUCHI PHARMACEUTICAL CO., LTD.
3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103 Japan

(assignee), desires to acquire the entire right, title, and interest in the application and invention, and to any United States patents to be obtained therefor;

Now therefore, for valuable consideration, receipt whereof is hereby acknowledged,

I/We, the above named assignor(s), hereby sell, assign and transfer to the above named assignee, its successors and assigns, the entire right, title and interest in the application and the invention disclosed therein for the United States of America, including the right to claim priority under 35 U.S.C. §119, and I/we request the Commissioner of Patents to issue any Letters Patent granted upon the invention set forth in the application to the assignee, its successors and assigns; and I/we will execute without further consideration all papers deemed necessary by the assignee in connection with the United States application when called upon to do so by the assignee.

I/We hereby authorize and request my attorneys SUGHRUE, MION, ZINN, MACPEAK & SEAS of 2100 Pennsylvania Avenue, N.W., Washington, D.C. 20037-3202 to insert here in parentheses (Application number 08/860,377, filed June 25, 1997) the filing date and application number of said application when known.

Date: July 28, 1997 s/ Makoto TAKEUCHI

Date: July 28, 1997 s/ Ryo NAITO

Date: July 28, 1997 s/ Masahiko HAYAKAWA

Date: July 28, 1997 s/ Yoshinori OKAMOTO

Date: July 28, 1997 s/ Yasuhiro YONETOKU

Date: July 28, 1997 s/ Ken IKEDA

ATTACHMENT 2

US006017927A

United States Patent [19]

Takeuchi et al.

[11] Patent Number: 6,017,927

[45] Date of Patent: Jan. 25, 2000

[54] **QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF**

[75] Inventors: **Makoto Takeuchi; Ryo Naito; Masahiko Hayakawa; Yoshinori Okamoto; Yasuhiro Yonetoku,** all of Ibaraki; **Ken Ikeda,** Chiba; **Yasuo Isomura,** Ibaraki, all of Japan

[73] Assignee: **Yamanouchi Pharmaceutical Co., Ltd.,** Tokyo, Japan

[21] Appl. No.: **08/860,377**

[22] PCT Filed: **Dec. 27, 1995**

[86] PCT No.: **PCT/JP95/02713**

§ 371 Date: **Aug. 28, 1997**

§ 102(e) Date: **Aug. 28, 1997**

[87] PCT Pub. No.: **WO96/20194**

PCT Pub. Date: **Jul. 4, 1996**

[30] **Foreign Application Priority Data**

Dec. 28, 1994 [JP] Japan 6-327045

[51] **Int. Cl.**[7] **A61K 31/435**; C07D 453/02

[52] **U.S. Cl.** **514/305**; 546/137

[58] **Field of Search** 546/137; 514/305

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

A20309424	3/1989	European Pat. Off. .
A1424021	4/1991	European Pat. Off. .
A10247266	12/1997	European Pat. Off. .
7-06635	3/1995	Japan .
7258250	10/1995	Japan .
A2249093	4/1992	United Kingdom .
WO9206958	4/1992	WIPO .
WO9316048	8/1993	WIPO .

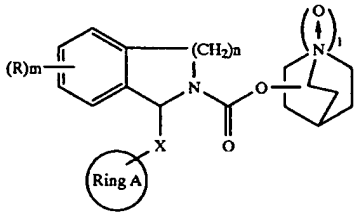
Primary Examiner—Patricia L. Morris

Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas, PLLC

[57] **ABSTRACT**

Quinuclidine derivatives represented by general following general formula (I), salts, N-oxides or quaternary ammonium salts thereof, and medicinal compositions containing the same.

(I)



The compound has an antagonistic effect on muscarinic M_3 receptors and is useful as a preventive or remedy for urologic diseases, respiratory diseases or digestive diseases.

7 Claims, No Drawings

QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

TECHNICAL FIELD

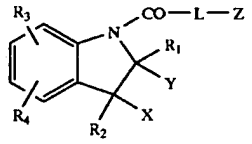
This invention relates to medicines, particularly quinuclidine derivatives or their salts, or quaternary ammonium salts having muscarinic receptor antagonistic activities and also to pharmaceutical compositions containing such compounds.

BACKGROUND ART

Studies have been made on the muscarinic receptor, and it is known that compounds having muscarinic receptor antagonistic activities cause bronchodilation, suppression of gastrointestinal motility, suppression of acid secretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia, or the like. It is known that the muscarinic receptor includes at least three subtypes. The M_1 receptor mainly exists in the brain or the like, the M_2 receptor in the heart or the like, and the M_3 receptor in the smooth muscles or gland tissues.

A number of such compounds having muscarinic receptor antagonistic activities are hitherto known and, for example, atropine is a typical example ("The MERCK INDEX, ELEVENTH EDITION", p. 138). However, atropine antagonizes the M_1, M_2 and M_3 receptors non-selectively, so that it is difficult to use it for the treatment of a specific disease. In recent years, according to the progress of the studies on the subtypes of the muscarinic receptor, compounds having selective antagonistic activities against the M_1, M_2 or M_3 receptor have been investigated (an unexamined published British Patent Application No. 2,249,093, an unexamined published Japanese Patent Application (kokai) 1-131145, and an unexamined published Japanese Patent Application (kokai) 3-133980). There is a demand for a compound having selective antagonistic activity against muscarinic M_3 receptor among these three subtypes and is free from the cardiac side effects resulting from the M_2 receptor.

The compound represented by the following general formula is described in an unexamined published Japanese Patent Application (kokai) 62-252764.

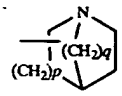


(wherein L represents NH or O;

X and Y each independently represents a hydrogen atom or a C_{1-6} alkyl group or they may be combined together to form a bond;

R_1 and R_2 each independently represents a hydrogen atom, a C_{1-6} alkyl group . . . (omission) . . . ;

R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, CF_3, a C_{1-6} alkyl group . . . (omission) . . . , a phenyl group, an amino group which may optionally be N-substituted by one or two groups selected from phenyl, C_{1-6} alkyl groups or may optionally be N-disubstituted by C_{6-8} polyethylene . . . (omission) . . . ;



p is 1 or 2; and q is 1–3.

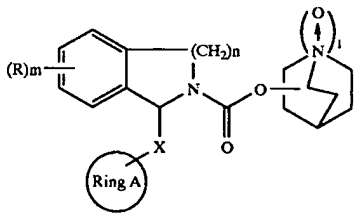
The compound described in the above patent literature is disclosed as a 5-HT antagonist and no disclosure about the muscarinic receptor antagonistic activity is found. The above compound is clearly distinguished from the compound according to the present invention in pharmacological effects.

DISCLOSURE OF THE INVENTION

The inventors of the present application have carried out extensive studies on compounds having the above-described muscarinic M_3 receptor antagonistic activities. As a result, we created novel quinuclidine derivatives having a basic skeleton different from that of the conventional compound, and found that such compounds have excellent selective antagonistic activity against muscarinic M_3 receptor, resulting in the completion of the present invention.

Thus, the compounds of the present invention relate to quinuclidine derivatives represented by the following general formula (I); their salts, or quaternary ammonium salts; pharmaceutical compositions comprising said compounds or salts thereof and pharmaceutically acceptable carriers, particularly to muscarinic M_3 receptor antagonists.

(I)



(symbols in the formula have the following meanings:

Ring A: an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, wherein said ring may be substituted by an optional substituent;

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1,

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2, hereinafter the same apply similarly)

Among the compound (I) of the present invention, particularly preferred compounds are quinuclidine derivatives wherein the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which such a ring may be substituted by a substituent selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono-or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group, and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group, and their salts, or quaternary ammonium salts;

quinuclidine derivatives wherein R represents a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which such a ring may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and their salts, or quaternary ammonium salts;

quinuclidine derivatives wherein m is 0, and the ring A represents an aryl group, a cycloalkyl group or a cycloalkenyl group which may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group or a lower alkoxy group, or a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and their salts, or quaternary ammonium salts;

quinuclidine derivatives wherein the ring A represents a phenyl group which may be substituted by a halogen atom or a lower alkyl group, a cycloalkyl group, a pyridyl group, a furyl group or a thienyl group, and their salts, or quaternary ammonium salts;

quinuclidine derivatives wherein X represents a single bond, and their salts, or quaternary ammonium salts; and

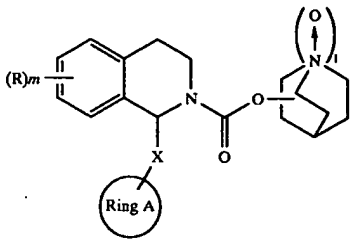
quinuclidine derivatives wherein n is 2, and their salts, or quaternary ammonium salts.

The present invention also provides muscarinic M_3 receptor antagonists which comprise quinuclidine derivatives (I) or their salts, or quaternary ammonium salts, that is, the compound (I) of the present invention and pharmaceutically acceptable carriers, preferably agents for the prevention and/or treatment of urinary diseases (e.g., neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis), or respiratory diseases (e.g., chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis).

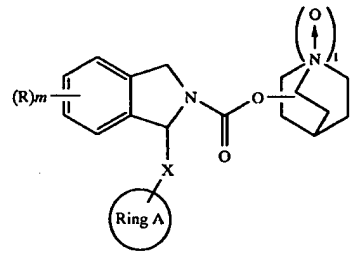
Hereinafter, the compound (I) of the present invention will be described in detail.

Different from the conventional muscarinic M_3 receptor antagonist, the compound (I) of the present invention is structurally characterized in that it has as a basic skeleton a tetrahydroisoquinoline skeleton (Ia) or isoindoline skeleton (Ib) having a quinuclidinyloxycarbonyl group, etc. bonded to the nitrogen atom in the ring as shown below.

(Ia)



(Ib)



Furthermore, the compound (I) of the present invention is characterized in that it has ring A, that is, a cyclic group selected from an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, at the 1-position of the tetrahydroisoquinoline or isoindoline through X.

Unless otherwise specified, the term "lower" as used in the definition of the general formula in this specification means a linear or branched carbon chain having 1 to 6 carbon atoms. Accordingly, the "lower alkyl group" means linear or branched alkyl group having 1 to 6 carbon atoms. Specific examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl groups. Among these groups, alkyl groups having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl groups are preferred, and a methyl group is more preferred.

The "aryl group" means aromatic hydrocarbon groups and preferably aryl groups having 6 to 14 carbon atoms. Specific examples include phenyl, naphthyl, indenyl, anthryl and phenanthryl groups, and a phenyl group is more preferred.

Examples of the "cycloalkyl group" include those having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Among these groups, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups are preferred, and a cyclohexyl group is more preferred.

Examples of the "cycloalkenyl group" include those having 3 to 8 carbon atoms such as 1-cyclopropenyl, 2-cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cyloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 4-cycloheptenyl, 1-cyclooctenyl, 2-cyclooctenyl, 3-cyclooctenyl, 4-cyclooctenyl, 2,4-cyclopentadienyl, 2,5-cyclohexadienyl, 2,4-cycloheptadienyl, and 2,6-cycloheptadienyl.

The "heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom" means a 5- or 6-membered heteroaryl group which may be condensed with a benzene ring. Specific examples include 5- or 6-membered monocyclic heteroaryl groups containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, such as furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl groups; and 5- or 6-membered heteroaryl groups condensed with a benzene ring, such as indolyl, indazolyl, indolizinyl, quinolyl, quinazolinyl, quinolizinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzoisoxazolyl, benzooxazolyl, benzothiazolyl and benzothienyl groups.

Among these groups, preferred are 5- or 6-membered monocyclic heteroaryl groups containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and furyl, thienyl and pyridyl groups are more preferred.

The "5- to 7-membered saturated heterocyclic group" means a 5-, 6- or 7-membered saturated heterocyclic group containing 1 to 2 oxygen, nitrogen and/or sulfur atoms. Specific examples include pyrrolidinyl, imidazolydinyl, piperidinyl, piperazinyl and morpholinyl groups.

The "aryl group", "cycloalkyl group", "cycloalkenyl group", "heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom", "5- or 6-membered monocyclic heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom", or "5- to 7-membered saturated heterocyclic group" as the group A may be substituted by an optional substituent. The number of the substituent is not limited to one but may be plural. Any group that can substitute for such a ring can be employed as the optional substituent. Preferred examples include a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxyl group, an amino group or a mono- or di-lower alkylamino group; a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group and a mono- or di-lower alkylamino group are more preferred; a halogen atom, a lower alkyl group, a hydroxyl group and a lower alkoxy group are still more preferred; and a halogen atom and a lower alkyl group are particularly preferred.

Examples of the halogen-atom include fluorine, chlorine, bromine and iodine. When the substituent is a halogen atom, the number of the substituents is not particularly limited. When two or more halogen atoms are substituted, any combination of the above atoms is possible. Examples of the halogen atom-substituted lower alkyl group include fluoromethyl, chloromethyl, bromomethyl, iodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 2-chloroethyl, 2-bromoethyl, dichloromethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl and dichlorobromomethyl. Among these groups, a trifluoromethyl group is preferred.

Examples of the "lower alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy (amyloxy), isopentyloxy, tert-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and hexyloxy. Among these groups, lower alkoxy groups containing an alkyl group having 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy and butoxy are preferred, and methoxy and ethoxy groups are more preferred.

Examples of the lower alkoxycarbonyl group include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxy (amyloxy)carbonyl, isopentyloxycarbonyl, tert-pentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl, 1,2-dimethylpropoxycarbonyl, 1-ethylpropoxycarbonyl and hexyloxycarbonyl.

Examples of the "lower acyl group" include formyl, acetyl, propionyl, butyryl, valeryl and pivaloyl, and formyl, acetyl and propionyl are preferred.

The "lower alkylthio group" means a mercapto group of which hydrogen atom has been substituted by the above-exemplified lower alkyl group, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio and hexylthio groups.

Examples of the "lower alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, pentylsulfonyl and hexylsulfonyl.

Examples of the "lower alkylsulfinyl group" include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl and hexylsulfinyl.

Examples of the "lower alkanesulfonamido group" include methanesulfonamido, ethanesulfonamido, propanesulfonamido, isopropanesulfonamido, butanesulfonamido, pentanesulfonamido and hexanesulfonamido.

The "mono- or di-lower alkylcarbamoyl group" means a carbamoyl group in which one or two hydrogen atom(s) have been substituted by the above-exemplified lower alkyl group(s), such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl and dimethylcar-bamoyl groups.

The "mono- or di-lower alkylamino group" means an amino group in which one or two hydrogen atom(s) have been substituted by the above-exemplified lower alkyl group (s), such as methylamino, ethylamino, propylamino, dimethylamino, diethylamino and dipropylamino groups.

The term "lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group" means a lower alkyl group in which at least one optional

hydrogen atom has been substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group. The lower alkyl group substituted by a halogen atom is as described in the above description of the halogen atom.

The compound (I) of the present invention contains a quinuclidinyl group. The nitrogen atom of the quinuclidinyl group may form oxide (l=1) or quaternary ammonium salt. Where a quaternary ammonium salt is formed, specific examples of the group bound to the nitrogen atom include lower alkyl, lower alkenyl and lower alkynyl.

The term "lower alkeny" as used herein means a linear or branched alkenyl group having 2 to 6 carbon atoms, such as vinyl, propenyl, butenyl, methylpropenyl, dimethylvinyl, pentenyl, methylbutenyl, dimethylpropenyl, ethylpropenyl, hexenyl, dimethylbutenyl and methylpentenyl. Among these groups, a propenyl group is preferred.

The "lower alkynyl group" means a linear or branched alkynyl group having 2 to 6 carbon atoms, such as ethynyl, propynyl, butynyl, methylpropynyl, pentynyl, methylbutynyl and hexynyl groups. Among these groups, alkynyl groups having 2 to 3 carbon atoms such as ethynyl and propynyl are preferred.

The anion for the quaternary ammonium salt is not particularly limited and the examples include ions of a halogen atom, triflate, tosylate and mesylate, preferably ions of a halogen atom, i.e. halide ions (e.g., chloride ion, bromide ion, iodide ion and triiodide ion). Examples of other anions include inorganic anions such as nitrate ion, sulfate ion, phosphate ion and carbonate ion, carboxylates such as formate ($HCOO^-$), acetate (CH_3COO^-), propionate, oxalate and malonate, and amino acid anions such as glutamate. Among the halide ions, bromide ion and iodide ion are preferred. Incidentally, the anion can be converted into a preferable anion as needed by the ordinary ion exchange reaction.

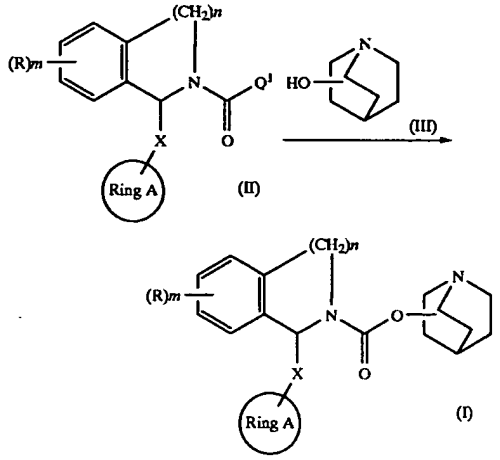
The compound (I) of the present invention contains an asymmetric carbon atom so that there exist optical isomers based on it. In addition, some of the invention compounds have stereoisomers or tautomers. The present invention also embraces diastereomers and enantiomers obtained by the separation of the above isomers as well as mixtures thereof.

Some of the compounds (I) of the present invention can form salts with an acid as well as the above-described quaternary ammonium salts with a quinuclidynyl group. Examples of such salt include acid addition salts with a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid or phosphoric acid; and those with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid or glutamic acid. The compounds (I) of the present invention also embrace hydrates, solvates with ethanol or the like, and substances in any polymorphism crystals.

(Preparation Process)

The compound (I) of the present invention can be prepared in accordance with various processes. The typical preparation processes are explained below.

First Preparation Method



(in the formula, Q^1 represents a leaving group which is advantageous in the present reaction, and ring A, R, X, m and n have the same meanings as defined above. Hereinafter, the same will apply similarly).

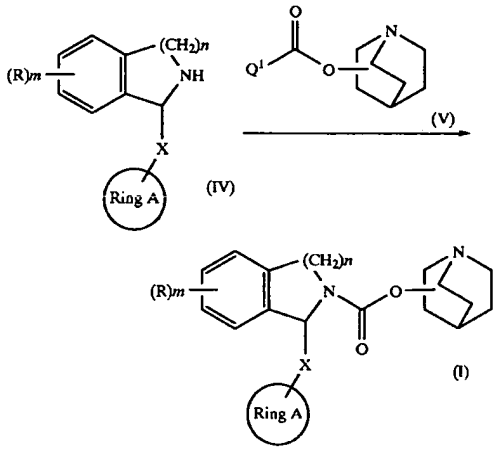
This reaction is carried out by stirring the compound represented by the general formula (II) and quinuclidinol represented by the general formula (III) in an amount corresponding to the reaction in an inert solvent at room temperature or under heating.

The leaving group Q^1 embraces, for example, a halogen atom, a lower alkoxy group, a phenoxy group and an imidazolyl group.

Examples of the inert solvent include dimethylformamide (DMF), dimethylacetamide, tetrahydrofuran (THF), dioxane, dimethoxyethane, diethoxyethane, benzene, toluene and xylene and mixed solvents thereof.

It is preferable to add a base (e.g., sodium, sodium hydride, sodium methoxide and sodium ethoxide) in order to accelerate the present reaction.

Second Preparation Method



(wherein the ring A, R, X, m, n and Q^1 have the same meanings as defined above.)

This reaction is carried out by stirring the compound represented by the general formula (IV) and the compound

represented by the general formula (V) in the above-described inert solvent at room temperature or under heating.

It is preferable to add a base (e.g., sodium, sodium hydride, sodium methoxide, sodium ethoxide, triethylamine and pyridine) in order to accelerate the present reaction.

(Other Preparation Methods)

Among the compounds of the present invention, a compound in which the nitrogen atom of the quinuclidinyl group forms oxide or a quaternary ammonium salt can be prepared by N-oxide formation or N-alkylation of a tertiary amine compound in the compounds of the present invention.

The N-oxide formation reaction can be carried out by the oxidation reaction in a conventional manner, more specifically, by stirring a tertiary amine compound in the compounds of the present invention and a corresponding amount or excess amount of oxidizing agent in an inert solvent such as chloroform, dichloromethane or dichloroethane, an alcohol such as methanol or ethanol or water or a mixed solvent thereof under cooling or at room temperature, or in some cases under heating. Examples of the oxidizing agent include organic peracids such as m-chloroperbenzoic acid, sodium periodate and hydrogen peroxide.

The N-alkylation reaction can be carried out in accordance with the conventional N-alkylation reaction, more specifically by stirring a tertiary amine compound in the compound of the present invention and a corresponding amount of an alkylating agent in an inert solvent such as dimethylformamide, chloroform, benzene, 2-butanone, acetone or tetrahydrofuran under cooling or a room temperature, or in some cases under heating.

Examples of the alkylating agent include lower alkyl halides, lower alkyl trifluoromethanesulfonates, lower alkyl p-toluenesulfonates and lower alkyl methanesulfonates, preferably lower alkyl halides.

For the preparation of the compound of the present invention, it is sometimes necessary to protect a functional group. In such a case, introduction of a proper protecting group and deprotection operation in a conventional manner are carried out additionally.

The compound of the present invention so prepared is provided as is in the free form, or after subjected to the salt formation treatment in a conventional manner, it is isolated and purified as its salt. Isolation and purification are carried out by the ordinary chemical operation such as extraction, concentration, evaporation, crystallization, filtration, recrystallization or a variety of chromatography.

Industrial Applicability

The compound of the present invention has affinity and selectivity for the muscarinic M_3 receptor and, as an M_3 receptor antagonist, it is useful as an agent for prevention or treatment of various M_3 receptor-related diseases, particularly urinary diseases such as urinary incontinence or pollakiuria in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm or chronic cystitis; respiratory diseases such as chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis; or digestive diseases such as irritable bowel syndrome, spastic colitis or diverticulitis.

In particular, the compound of the present invention has high selectivity for the M_3 receptor existing in the smooth muscle or gland tissues compared with the M_2 receptor existing in the heart or the like, so that it has high utility as an M_3 receptor antagonist having less side effects on the heart or the like, particularly as an agent for prevention or treatment of urinary incontinence, pollakiuria, chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis.

The affinity and antagonism of the compound of the present invention for the muscarinic receptor was confirmed by the following tests.

Muscarinic Receptor Binding Test (in vitro)

a. Preparation of Membranes

From a male Wistar rat (Japan SLC), the heart and submandibular gland were excised, mixed with a 20 mM HEPES buffer (pH 7.5, which will hereinafter be abbreviated as "HEPES buffer") containing 5 times the volume of 100 mM sodium chloride and 10 mM magnesium chloride was added, followed by homogenization under ice-cooling. The resulting mixture was filtered through gauze, followed by ultracentrifugation at 50,000×g and 4° C. for 10 minutes. The precipitate obtained was suspended in an HEPES buffer, followed by further ultracentrifugation at 50,000×g and 4° C. for 10 minutes. The precipitate obtained was suspended in an HEPES buffer. The resulting suspension was stored at −80° C. and provided for the test after melting upon use.

b. Muscarinic M_2 Receptor Binding Test

The test was carried out in accordance with the method of Doods et al. (*J. Pharmacol. Exp. Ther.*, 242, 257–262, 1987) with some modifications. The cardiac membrane sample, [^{3}H]-quinuclidinyl benzilate and the test compound were incubated in a 0.5 ml HEPES buffer at 25° C. for 45 minutes, followed by suction filtration through a glass filter (Whatman GF/B). The filter was washed three times with 5 ml portions of an HEPES buffer. The radioactivity of the [^{3}H]-quinuclidinyl benzilate adsorbed on the filter was measured by a liquid scintillation counter. Incidentally, nonspecific binding of the receptor was determined by the addition of 1 μM atropine. The binding of the compound of the present invention for the muscarinic M_2receptor was determined from a dissociation constant (Ki) calculated, in accordance with Chen and Prusoff (*Biochem. Pharmacol.* 22, 3099, 1973), based on the concentration (IC_{50}) of the test compound at which 50% of the binding of the [^{3}H]-quinuclidinyl benzilate, that is, a labeled ligand was inhibited.

c. Muscarinic M_3 Receptor Binding Test

In a similar manner to the above muscarinic M_2 receptor binding test except that the submandibular gland was used as a membrane sample and [^{3}H]-N-methylscopolamine was used as a labeled ligand, a muscarinic M_3 receptor binding test was carried out.

Results: The compound (I) of the present invention had a Ki value of from 10^{-8} to 10^{-10} for M_3 receptor, which suggested that the affinity for M_3 receptor was at least 10 times as high as that for M_2 receptor.

Muscarinic Receptor Antagonism Test (in vivo)

a. Test on Rhythmic Bladder Contraction in Rat

A female Wistar rat (130–200 g) was subjected to urethane anesthesia (1.0 g/kg s.c.), followed by ligation of the ureter on the kidney side. A urethral catheter was allowed to remain in the bladder, and about 1.0 ml of physiological saline was injected into the bladder through the catheter to cause rhythmic bladder contraction. Intravesical pressure was measured by a pressure transducer. After rhythmic contraction continued stable for at least 5 minutes, the test compound was cumulatively administered from the external jugular vein. Five to ten minutes later, the intravesical pressure was measured. An inhibition ratio of bladder contraction was determined compared with the bladder contraction before administration of the test compound and the dose of the test compound required for 30% inhibition of the bladder contraction before administration was designated as ED_{30}.

As a result of the test, the compound of the present invention showed good ED_{30} value.

b. Test on Salivary Secretion in Rat

A male Wistar rat (160–190 g) was subjected to anesthesia with urethane (0.8 g/kg i.p.), and the test compound was administered (to the control group: solvent). Fifteen minutes later, 0.8 μmol/kg of oxotremorine was administered. In each case, the drug was administered through its femoral artery. The saliva secreted for 5 minutes after the administration of oxotremorine was collected and weighed. The inhibition ratio against the amount of saliva in the control group was determined and the dose of the test compound required for 50% inhibition of the amount of saliva in the control group was designated as ID_{50}.

As a result of the test, the ID_{50} value of atropine tested as a comparative compound was substantially the same with the ED_{30} value obtained in the above rat rhythmical bladder contraction test, while the ID_{50} value of the invention compound was at least 5 times as much as the above-described ED_{30} value, which suggested that the compound of the present invention has relatively weak action against the salivary secretion.

c. Test on Bradycardia in Rat

The test was carried out in accordance with the method of Doods et al. (*J. Pharmacol. Exp. Ther.*, 242, 257–262, 1987). A male Wistar rat (250–350 g) was subjected to anesthesia with pentobarbital sodium (50 mg/kg i.p.). The neck region was excised, followed by the division of right and left vagus nerves. After a cannula was inserted into a trachea to secure airway, a stainless rod was inserted from the orbit and the spinal cord was destroyed. Under artificial respiration (at 10 cc/kg and 50 times/minute), the rectal temperature was maintained at 37.5° C. and a heart rate was monitored at the common carotid artery. An indwelling needle was fixed to the femoral artery, from which the drug was administered. After the destruction of the spinal cord, the rat was allowed to stand for 15 minutes to attain the equilibrium, followed by the administration of atenolol (10 mg/kg). After the equilibration for additional 15 minutes, the test compound was administered. Fifteen minutes later, oxotremorine was cumulatively administered, thereby the reduction in the heart rate was measured. The amount of the test compound required for 10-times rightward shift of the dose-response curve of the control group was designated as DR_{10}.

Results: The compound (I) of the present invention had sufficiently low activity against bradycardia and no bradycardia was observed at the-administration amount of several mg/kg.

As a result of the above-described muscarinic receptor binding test (in vitro), it was found that the compound (I) of the present invention had selectivity and high affinity for M_3 receptor. Even in the muscarinic receptor antagonism test (in vivo), the compound of the present invention showed good muscarinic M_3 antagonistic activity but low activity on the bradycardia having relationship with muscarinic M_2 receptor. Accordingly, it was found that the compound (I) of the present invention has selective antagonistic activity against muscarinic M_3 receptor, and furthermore, it has less side effects such as dry mouth compared with the conventional anti-cholinergic agent.

A pharmaceutical composition containing one or more of the compounds of the present invention and salts thereof is prepared using an ordinary pharmaceutically acceptable carrier.

In the present invention, the administration of the pharmaceutical composition can be carried out either orally or parenterally in the form of an injection, suppository, transdermal agent, inhalant or intravesical injection.

The dose is optionally determined in each case in consideration of the conditions, age, sex and the like of the patient to be administered. In the oral administration, the daily dose may generally range from about 0.01 mg/kg to 100 mg/kg per adult. It is administered once or in 2–4 portions. Where intravenous administration is adopted in consideration of the conditions of the patient, the daily dose may generally range from about 0.001 mg/kg to 10 mg/kg per adult, once or plural portions per day.

Examples of the pharmaceutical carrier include nontoxic solid or liquid pharmaceutical substances.

Examples of the solid composition for the oral administration include tablets, pills, capsules, powders and granules, or the like. In such solid compositions, one or more active substances are mixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, agar, pectin, magnesium metasilicate or magnesium aluminate. In the composition, it is possible to incorporate additives other than the above inert diluent, for example, a lubricant such as magnesium stearate, a disintegrator such as cellulose calcium glycolate, a stabilizer such as lactose, a solubilization aid such as glutamic acid or aspartic acid in a conventional manner. A tablet or pill may optionally be coated with sugar or a film of a gastric or enteric substance such as sucrose, gelatin, hydroxypropylcellulose or hydroxypropylmethylcellulose phthalate.

Examples of the liquid-composition for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs which contain a commonly employed inert diluent such as purified water or ethanol. The composition can also contain, in addition to such an inert diluent, a wetting agent, auxiliary agent such as suspending agent, sweetener, flavoring agent, aroma and/or antiseptic.

The injection for parenteral administration according to the present invention include a sterile aqueous or nonaqueous solution, suspension or emulsion. Examples of the aqueous solution and suspension include distilled water and physiological saline for injection. Examples of the non-water-soluble solution or suspension include ethylene glycol, polypropylene glycol, polyethylene glycol, vegetable oils such as cacao butter, olive oil or sesame oil, alcohols such as ethanol, gum arabic and "Polysolvate 80" (trade name). Such a composition may further contain an isotonicity agent, antiseptic agent, wetting agent, emulsifying agent, dispersing agent, stabilizer (for example, lactose) and/or solubilizing aid (for example, glutamic acid, aspartic acid). They are sterilized by, for example, filtration through a bacteria-retaining filter, incorporation of a sterilizer, or irradiation. Alternatively, a sterile solid composition which has been prepared in advance is dissolved in sterile water or a sterile injection solvent upon use.

BEST MODES FOR CARRYING OUT THE INVENTION

The present invention will hereinafter be described in further detail with reference to the following Examples. However, the compounds of the present invention should not be construed as being limited to the compounds which will be described later in Examples but embrace all the compounds represented by the above formula (I) and salts, hydrates, solvates, geometrical and optical isomers and any polymorphism forms of the compound (I).

Incidentally, the starting compounds for the compound of the present invention include novel compounds and prepa-

ration examples of such starting compounds will be described below as Reference Examples.

REFERENCE EXAMPLE 1

To a 130 ml dichloromethane solution containing 6.28 g of 1-phenyl-1,2,3,4-tetrahydroisoquinoline and 3.34 g of triethylamine, 3.1 ml of ethyl chloroformate was added dropwise under ice-cooling, followed by stirring at room temperature overnight. The reaction solution was washed successively with water, 1N hydrochloric acid, water and brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, thereby 10.58 g of ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as pale yellow oil.

Infrared absorption spectrum vmax(neat)cm^{-1}: 1700, 1430, 1296, 1230, 1122. Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.29 (3H, t, J=7.3 Hz), 2.75–3.45 (3H, m), 3.90–4.40 (1H, m), 4.21 (2H, q, J=7.3 Hz), 6.38 (1H, s), 6.95–7.45 (9H, m).

In a similar manner to Reference Example 1, the compounds of the following Reference Examples 2 to 14 were obtained.

REFERENCE EXAMPLE 2

Methyl 1-phenyl-2-isoquinolinecarboxylate

Starting compounds: 1-phenylisoindoline, methyl chloroformate

Infrared absorption spectrum vmax(KBr)cm^{-1}: 1708, 1460, 1376, 1100 Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 3.60, 3.72 (3H, s×2), 4.89, 4.96 (2H, s×2), 5.94, 6.03 (1H, s×2), 6.95–7.10 (1H, m), 7.15–7.35 (8H, m)

REFERENCE EXAMPLE 3

Ethyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-pyridyl)-1,2,3,4-tetrahydroisoquinoline

Properties: pale yellow oil

Mass analysis (m/z, EI): 282 (M^+); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.29 (3H, t, J=7.1 Hz), 2.60–3.45 (3H, m), 3.85–4.20 (1H, m), 4.22 (2H, q, J=7.1 Hz), 6.31 (1H, s), 7.14 (2H, dd, J=4.4, 1.5 Hz), 7.17–7.26 (4H, m), 8.51 (2H, dd, J=4.4, 1.5 Hz)

REFERENCE EXAMPLE 4

Ethyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(2-thienyl) isoquinoline

Properties: pale yellow oil

Mass analysis (m/z, EI): 287 (M^+); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.32 (3H, t, J=7.3 Hz), 2.65–3.60 (3H, m), 4.00–4.30 (1H, m), 4.23 (2H, q, J=7.3 Hz), 6.53 (1H, s), 6.70–6.95 (2H, m), 7.15–7.30 (5H, m)

REFERENCE EXAMPLE 5

Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(3-thienyl)-isoquinoline

Properties: Orange oil

Mass analysis (m/z, FAB): 288 (M^++1); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.2–1.3 (3H, m), 2.7–2.8 (1H, m), 2.9–3.0 (1H, m), 3.1–3.3 (1H, m), 3.9–4.2 (3H, m), 6.2–6.4 (1H, m), 6.83 (1H, s), 6.95–7.26 (6H, m)

REFERENCE EXAMPLE 6

Ethyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(2-furyl)-1,2,3,4-tetrahydroisoquinoline

Mass analysis (m/z, EI): 271 (M^+); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.30 (3H, t, J=6.5 Hz), 2.75–2.85 (1H, m), 2.90–3.10 (1H, m), 3.20–3.50 (1H, m), 4.05–4.35 (4H, m), 6.00 (1H, s), 6.20–6.45 (2H, m), 7.15–7.25 (4H, m), 7.33 (1H, s)

REFERENCE EXAMPLE 7

(1R)-Ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline

Elemental analysis (for $C_{18}H_{19}NO_2$);

	C (%)	H (%)	N (%)
Calcd.:	76.84	6.81	4.98
Found:	76.53	6.82	4.93

Specific optical rotation $[\alpha]_D^{25}$: 199.2 (C=1.03,$CHCl_3$)

Mass analysis (m/z, FAB): 282 (M^++1)

REFERENCE EXAMPLE 8

(1S)-Ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline

Elemental analysis (for $C_{18}H_{19}NO_2$)

	C (%)	H (%)	N (%)
Calcd.:	76.84	6.81	4.98
Found:	76.64	6.82	4.99

Specific optical rotation $[a]^2D^5$: −200.9 (C=1.09, $CHCl_3$)

Mass analysis (m/z, EI): 281 (M^+)

REFERENCE EXAMPLE 9

Ethyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, EI): 315 (M^+); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS Internal standard); δ: 1.29 (3H, t, J=7.0 Hz), 2.70–3.52 (3H, m), 4.00–4.30 (1H, m), 4.20 (2H, q. J=7.0 Hz), 6.35 (1H, s), 7.05–7.35 (8H, m)

REFERENCE EXAMPLE 10

Ethyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, FAB): 300 (M^++1); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.30 (3H, t, J=8.9 Hz), 2.75 (1H, dd, J=12.5, 3.4 Hz), 2.9–3.1 (1H, m), 3.1–3.3 (1H, m), 4.0–4.3 (3H, m), 6.2–6.4 (1H, m), 6.93–7.03 (3H, m), 7.16–7.24 (5H, m).

REFERENCE EXAMPLE 11

Ethyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(4-tolyl) isoquinoline

Mass analysis (m/z, EI): 295 (M^+); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.20–1.35 (3H, m), 2.30 (3H, s), 2.70–2.80 (1H, m), 2.90–3.10 (1H, m), 3.23 (1H, t, J=10.0 Hz), 3.95–4.30 (3H, m), 6.29, 6.41 (1H, brs×2), 7.00–7.25 (8H, m).

REFERENCE EXAMPLE 12

Ethyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-benzyl-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, FAB): 296 (M^++1); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.02, 1.23 (3H, t×2, J=7.1 Hz), 2.63–3.20 (4H, m), 3.30–3.50 (1H, m), 3.75–4.25 (3H, m), 5.27, 5.38 (1H, t×2, J=6.8 Hz), 6.85–7.28 (9H, m).

REFERENCE EXAMPLE 13

Ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline

Properties: yellow oil

Mass analysis (m/z, FAB): 288 (M^++1); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 0.70–2.00 (11H, m), 1.26 (3H, t, J=7.3 Hz), 2.89 (2H, t, J=7.1 Hz), 3.25–4.20 (2H, m), 4.14 (2H, q, J=7.1 Hz), 4.65–4.95 (1H, m), 7.00–7.30 (4H, m).

REFERENCE EXAMPLE 14

Ethyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(3-furyl)-1,2,3,4-tetrahydroisoquinoline

Properties: yellow oil

Mass analysis (m/z, EI): 271 (M^+); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.31 (3H, t, J=7.0 Hz), 2.55–3.40 (3H, m), 3.90–4.30 (1H, m), 4.22 (2H, q, J=7.0 Hz), 6.20–6.45 (2H, m), 6.95–7.40 (6H, m).

The chemical structural formulas of the compounds obtained in Reference Examples 1–14 are shown in the following Tables 1–2.

TABLE 1

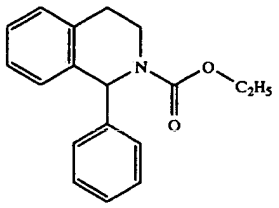
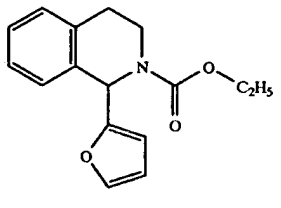
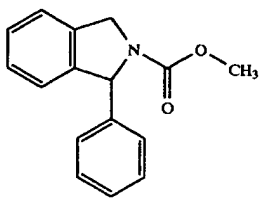
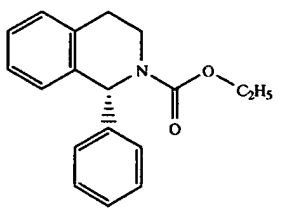
Reference Example No.	Structural Formula	Reference Example No.	Structural Formula
1		6	
2		7	

TABLE 1-continued

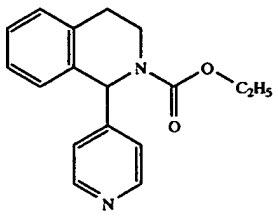
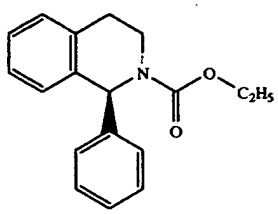
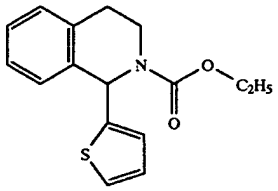
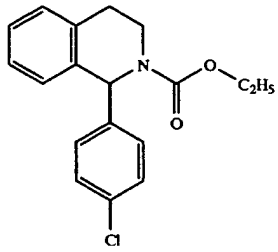
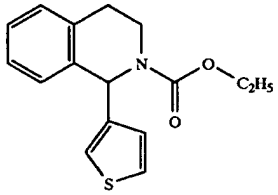
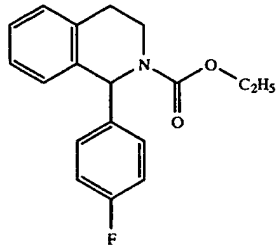
Reference Example No.	Structural Formula	Reference Example No.	Structural Formula
3		8	
4		9	
5		10	

TABLE 2

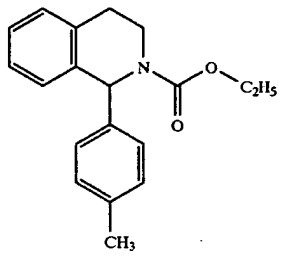
Reference Example No.	Structural Formula
11	

TABLE 2-continued

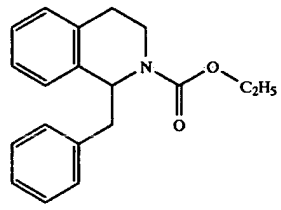
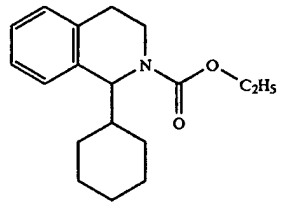
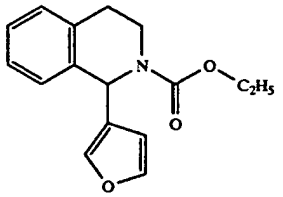
12	
13	

TABLE 2-continued

14	

EXAMPLE 1

To a 30 ml toluene solution containing 0.70 g of ethyl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate and 0.41 g of 3-quinuclidinol, 0.03 g of sodium hydride (60%) was added. The resulting mixture was stirred at 140° C. for 2 days while removing the ethanol formed. The reaction mixture was cooled to room temperature, brine was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform:methanol=10:1→chloroform:methanol:28% aqueous ammonia=10:1:0.1), thereby 0.11 g of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as yellow oil. The resulting oil was dissolved in 10 ml of ethanol, followed by the addition of 27 mg of oxalic acid. Then, the solvent was removed under reduced pressure. The resulting solid was recrystallized from isopropanol and isopropyl ether, thereby 0.08 g of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monooxalate was obtained as colorless crystals.

Melting point: 122–124° C. (i-PrOH-i-Pr_2O)

Elemental analysis (for $C_{25}H_{28}N_2O_6.0.75H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	64.43	6.38	6.01
Found:	64.25	6.15	5.88

In a similar manner to Example 1, the compound of Example 2 was obtained.

EXAMPLE 2

3-Quinuclidinyl 1-phenyl-2-isoindolinecarboxylate monohydrochloride

Starting compound: methyl 1-phenyl-2-isoindolinecarboxylate

Melting point: 164–165° C. (EtOH-Et_2O)

Elemental analysis (for $C_{22}H_{25}N_2O_2Cl.1.75H_2O$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	63.45	6.90	6.73	8.51
Found:	63.54	6.59	6.76	8.12

EXAMPLE 3

To a 50 ml toluene suspension containing 720 mg of ethyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and 973 mg of 3-quinuclidinol, 102 mg of sodium hydride (60%) was added at room temperature. The resulting mixture was heated under reflux for 5 hours and 40 minutes while the resulting ethanol was removed together with toluene. The reaction mixture was cooled to room temperature, followed by addition of 20 ml of water. The resulting mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure.

The resulting residue was purified by silica gel column chromatography (chloroform:methanol:28% aqueous ammonia=100:2:1), thereby 827 mg of 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate were obtained as yellow oil. The resulting oil was dissolved in 5 ml of ethyl acetate, 2 ml of a 4N hydrogen chloride in ethyl acetate solution was added. The solvent was then removed under reduced pressure. Ethanol and ether were added to the residue, and the crude crystals thus obtained was recrystallized from ethanol and ether, thereby 402 mg of 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate dihydrochloride was obtained as pale yellow crystals.

Melting point: 167–169° C. (EtOH-Et_2O)

Elemental analysis (for $C_{22}H_{27}N_3O_2Cl_2.2.2H_2O$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	55.51	6.65	8.83	14.90
Found:	55.46	6.98	8.64	14.84

In a similar manner to Example 3, the compounds of Examples 4 to 6 which will be described below were obtained.

EXAMPLE 4

3-Quinuclidinyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate monooxalate

Starting compound: Ethyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate

Elemental analysis (for $C_{23}H_{26}N_2O_6S.1.3H_2O$);

	C (%)	H (%)	N (%)	S (%)
Calcd.:	57.32	5.98	5.81	6.65
Found:	57.62	6.00	5.84	6.27

Mass analysis (m/z, FAB): 369 (M^++1)

EXAMPLE 5

(1RS,3'R)-3'-Quinuclidinyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate

Starting compounds: ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Properties: Brown oil

Elemental analysis (for $C_{21}H_{24}N_2O_2S.0.3H_2O$);

	C (%)	H (%)	N (%)	S (%)
Calcd.:	67.46	6.63	7.49	8.58
Found:	67.35	6.76	7.21	8.46

Mass analysis (m/z, FAB): 369 (M^++1)

EXAMPLE 6

3-Quinuclidinyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: Pale yellow oil

Elemental analysis (for $C_{21}H_{24}N_2O_3.0.5H_2O$);

	C (%)	H (%)	N (%)
Calcd.:	69.79	6.97	7.75
Found:	70.03	7.05	7.44

Mass analysis (m/z, FAB): 353 (M^++1)

EXAMPLE 7

To a 30 ml pyridine solution containing 2.09 g of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 2.26 g of 3-quinuclidinyl chloroformate monohydrochloride was added at room temperature, followed by stirring at 80° C. for 4 hours. Then, 0.12 g of 3-quinuclidinyl chloroformate monohydrochloride, followed by stirring at 80° C. for 4 hours. Then, 1.01 g of 3-quinuclidinyl chloroformate monohydrochloride was added, and the mixture was stirring at 80° C. for 25 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the residue, followed by washing with ethyl acetate twice. The resulting aqueous layer was adjusted to pH 9 with saturated sodium hydrogencarbonate aqueous solution, followed by extraction with ethyl acetate. After the organic layer was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, thereby 3.02 g of (1R,3'RS)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as yellow oil.

Mass analysis (m/z, FAB): 363 (M^++1); Nuclear magnetic resonance spectrum (DMSO-d_6, TMS internal standard); δ: 1.20–2.00 (5H, m), 2.40–2.95 (6H, m), 3.00–3.60 (3H, m), 3.80–3.95 (1H, m), 4.55–4.70 (1H, m), 6.25 (1H, brs), 7.05–7.35 (10H, m).

EXAMPLE 8

To a 120 ml toluene suspension containing 12.0 g of (1R)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and 16.27 g of (3R)-3-quinuclidinol, 1.69 g of sodium hydride (60%) was added at room temperature. The resulting mixture was heated for 3 hours while the resulting ethanol was removed together with toluene. The reaction mixture was cooled to room temperature, and 50 ml of brine was added, followed by extraction with ethyl acetate. The organic layer was washed with water and then extracted with 20% hydrochloric acid. The resulting aqueous layer was adjusted to pH 9 to 10 by adding a 1N aqueous solution of sodium hydroxide, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was dissolved in 140 ml of ethanol, and 10 ml of a 4N hydrogen chloride in ethyl acetate solution was added to the resulting solution. The solvent was then removed under reduced pressure. Acetonitrile and ether were added to the residue, and the resulting crude crystals were recrystallized from acetonitrile and ether, thereby 10.1 g of (1R,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride was obtained as colorless crystals.

Melting point: 212–214° C. (CH_3CN-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl$);

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	69.25	6.82	7.02	8.89
Found:	69.24	6.89	7.03	8.97

Specific optical rotation $[\alpha]_D^{25}$: 98.1 (C=1.00, EtOH)

In a similar manner to Example 8, the compounds of the following Examples 9 to 16 were obtained.

EXAMPLE 9

(1S,3'S)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3S)-3-quinuclidinol

Melting point: 211–212° C. (EtOH-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl.0.25H_2O$);

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	68.48	6.87	6.94	8.79
Found:	68.32	6.75	6.94	8.94

Specific optical rotation $[\alpha]_D^{25}$: −97.4 (C=0.50, EtOH)

EXAMPLE 10

(1S,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Melting point: 195–196° C. (EtOH-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl.0.25H_2O$);

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	68.48	6.87	6.94	8.79
Found:	68.73	6.88	6.95	8.70

Specific optical rotation $[\alpha]_D^{25}$: −151.2 (C=0.50, EtOH)

EXAMPLE 11

(1R,3'S)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1R)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3S)-3-quinuclidinol

Melting point: 194–195° C. (CH_3CN-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl$);

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	69.25	6.82	7.02	8.89
Found:	69.08	6.71	6.99	8.91

Specific optical rotation $[\alpha]_D^{25}$: 163.2 (C=0.50, EtOH)

EXAMPLE 12

3-quinuclidinyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monofumarate

Starting compounds: 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Melting point: 164–166° C. (EtOH-Et_2O)

Elemental analysis (for $C_{27}H_{29}N_2O_6Cl.0.5H_2O$);

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	62.13	5.79	5.37	6.79
Found:	62.19	5.68	5.23	6.49

EXAMPLE 13

(1RS,3'R)-3'-quinuclidinyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compounds: ethyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Properties: colorless oil

Elemental analysis (for $C_{23}H_{25}N_2O_2F.0.1H_2O$);

	C (%)	H (%)	N (%)	F (%)
Calcd.:	72.27	6.64	7.33	4.97
Found:	72.05	6.63	7.15	4.99

Mass analysis (m/z, FAB): 381 (M^++1)

EXAMPLE 14

3-quinuclidinyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Starting compounds: ethyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Properties: colorless oil

Elemental analysis (for $C_{24}H_{28}N_2O_2.0.8H_2O$);

	C (%)	H (%)	N (%)
Calcd.:	73.74	7.63	7.17
Found:	73.96	7.50	6.95

Mass analysis (m/z, FAB): 377 (M^++1)

EXAMPLE 15

3-Quinuclidinyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: pale yellow oil

Elemental analysis (for $C_{24}H_{28}N_2O_2.0.5H_2O$);

	C (%)	H (%)	N (%)
Calcd.:	74.78	7.58	7.26
Found:	74.95	7.83	7.18

Mass analysis (m/z, FAB): 377 (M^++1)

EXAMPLE 16

3-Quinuclidinyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compounds: ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: pale yellow amorphous

Elemental analysis (for $C_{23}H_{32}N_2O_2.0.3H_2O$);

	C (%)	H (%)	N (%)
Calcd.:	73.88	8.79	7.49
Found:	73.76	8.75	7.37

Mass analysis (m/z, FAB): 369 (M^++1)

EXAMPLE 17

In 12 ml of dichloromethane, 1.20 g of (1R,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was dissolved, 0.33 g of sodium hydrogencarbonate and 0.79 g of m-chloroperbenzoic acid (80%) were added under ice-cooling, followed by stirring at room temperature for one hour. Water was added to the reaction mixture and then the mixture was extracted with dichloromethane. The organic layer was washed with an aqueous solution of sodium thiosulfate and then dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform:methanol=20:1), thereby 0.43 g of (1'R,3R)-3-[[(1'-phenyl-1', 2',3',4'-tetrahydro-2'-isoquinolyl)carbonyl]oxy]quinuclidine 1-oxide was obtained.

Properties: white amorphous

Mass analysis (m/z, FAB): 379 (M^++1); Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard); δ: 1.85–2.15 (3H, m), 2.15–2.35 (2H, m), 2.75–2.90 (1H, m), 2.90–2.95 (1H, m), 3.20–3.50 (6H, m), 3.70–3.80 (1H, m), 3.85–4.10 (1H, m), 5.14 (1H, brs), 6.14, 6.43 (1H, brs ×2), 7.05–7.40 (9H, m).

EXAMPLE 18

To a 8 ml 2-butanone solution containing 1.04 g of (1R,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 0.18 ml of methyl iodide was added, followed by stirring at 55° C. for 40 minutes. After air cooling, the crystals precipitated were collected by filtration and then washed successively with 2-butanone and diethyl ether, thereby 0.93 g of (1'R,3R)-1-methyl-3-[[(1'-phenyl-1',2',3',4'-tetrahydro-2'-isoquinolyl)carbonyl]oxy]quinuclidinium iodide was obtained as colorless crystals.

Melting point: 202–203° C. (2-butanone)

Elemental analysis (for $C_{24}H_{29}N_2O_2I$)

	C (%)	H (%)	N (%)	I (%)
Calcd.:	57.15	5.79	5.55	25.16
Found:	57.17	5.71	5.51	25.15

In a similar manner to Example 8, the compound of the following Example 19 was obtained.

EXAMPLE 19

(1RS,3'R)-3'-quinuclidinyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: yellow oil

Elemental analysis (for $C_{21}H_{24}N_2O_3.0.3H_2O$);

	C (%)	H (%)	N (%)
Calcd.:	70.49	6.93	7.83
Found:	70.35	6.83	7.63

Mass analysis (m/z, EI): 352 (M^+)

The chemical structural formulas of the compounds obtained in Examples 1–19 are shown below in Tables 3–5.

TABLE 3

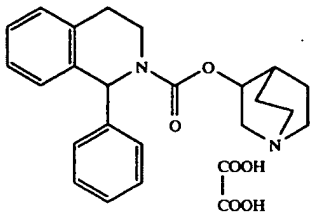
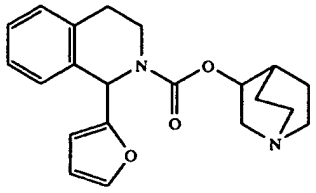
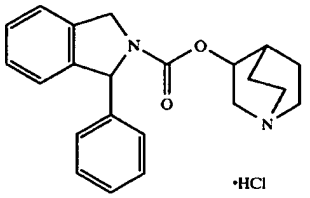
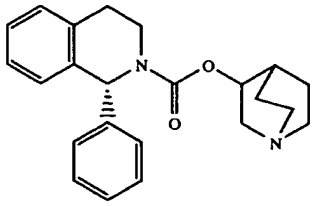
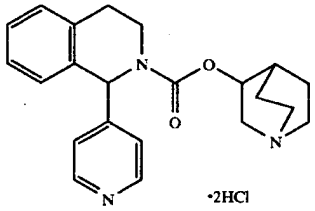
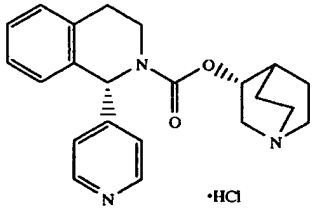
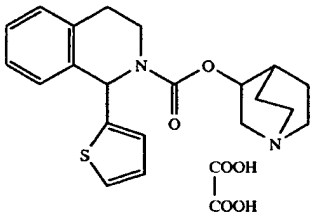
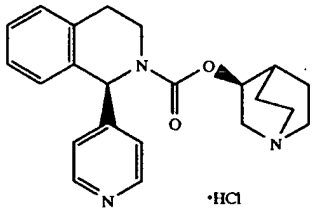
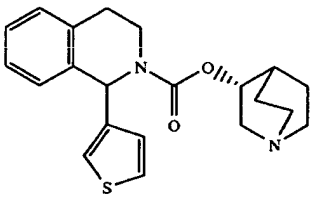
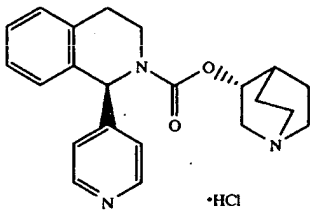
Example No.	Structural Formula	Example No.	Structural Formula
1		6	
2		7	
3		8	
4		9	
5		10	

TABLE 4

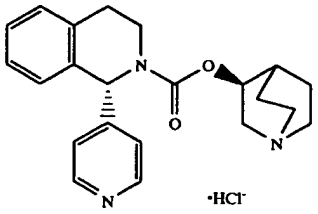
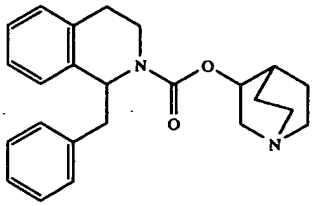
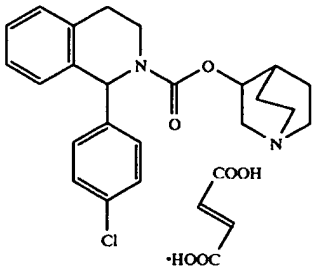
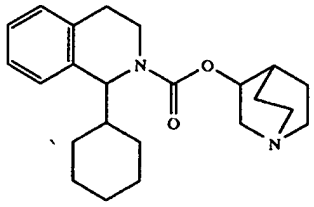
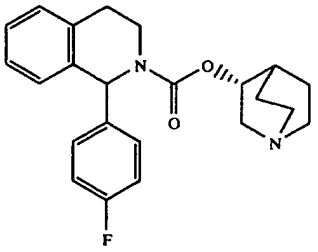
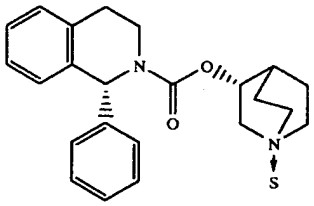
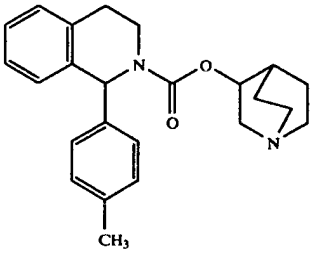
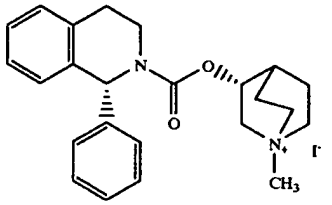
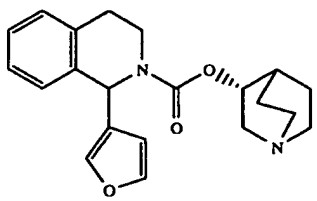
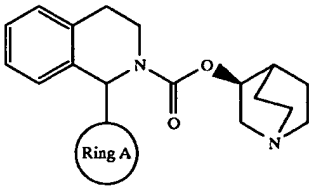
Example No.	Structural Formula	Example No.	Structural Formula
11		15	
12		16	
13		17	
14		18	

TABLE 5

Example No.	Structural Formula
19	

Each of the above-described compounds in Examples 3–6, 12–14, 16 and 19 can be obtained as an optical resolved form as shown in the following Tables 6–8 using an optically resolved intermediate in a similar manner to Examples 8–11.

TABLE 6



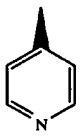
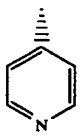
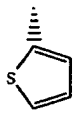
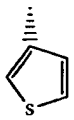
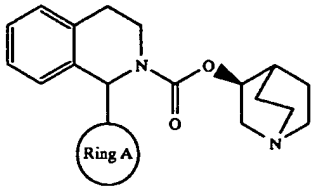
Example No.	Ring A	Example No.	Ring A
3-(a)		3-(b)	
4-(a)		4-(b)	
5-(a)		5-(b)	

TABLE 6-continued



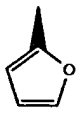
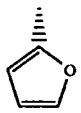
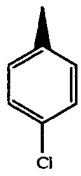
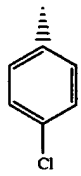
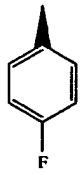
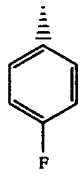
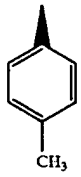
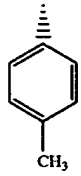
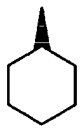
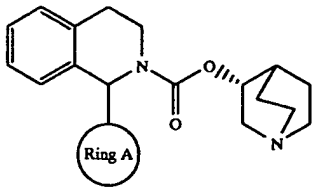
Example No.	Ring A	Example No.	Ring A
6-(a)		6-(b)	
12-(a)		12-(b)	
13-(a)		13-(b)	
14-(a)		14-(b)	
16-(a)		16-(b)	

TABLE 7



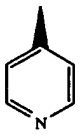
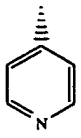
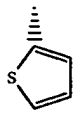
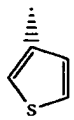
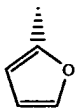
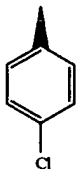
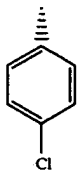
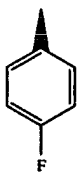
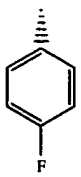
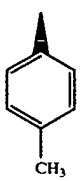
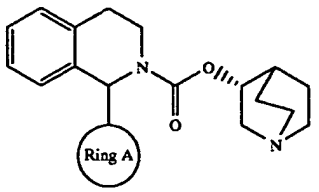
Example No.	Ring A	Example No.	Ring A
3-(c)		3-(d)	
4-(c)		4-(d)	
5-(c)		5-(d)	
6-(c)		6-(d)	
12-(c)		12-(d)	
13-(c)		13-(d)	
14-(c)		14-(d)	

TABLE 7-continued



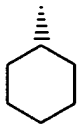
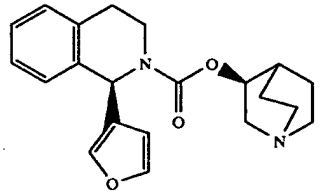
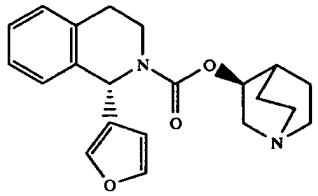
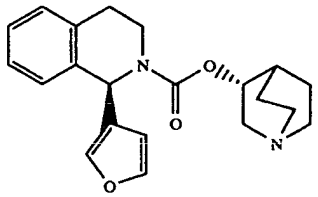
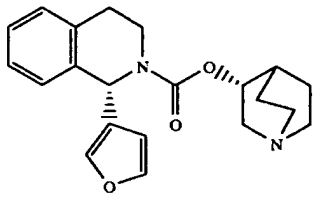
Example No.	Ring A	Example No.	Ring A
16-(c)		16-(d)	

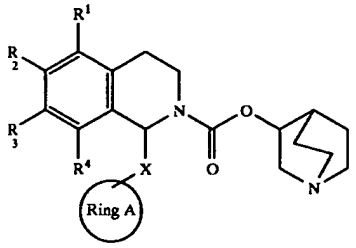
TABLE 8

Example No.	Structural Formula
19-(a)	
19-(b)	
19-(c)	
19-(d)	

The other compounds embraced by the present invention will be shown in Tables 9–33. They can be synthesized by

any one of the above-described preparation processes, processes described in Examples or processes known to those skilled in the art and do not require any particular experiment. Incidentally, these compounds are described as a racemic compound, but optical active substances based on an asymmetric carbon is also included.

TABLE 9



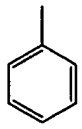
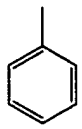
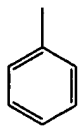
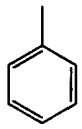
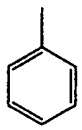
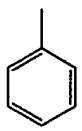
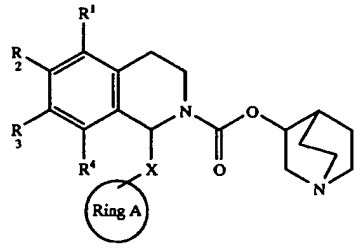
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-1	Cl	H	H	H	—	
A-2	H	H	Cl	H	—	
A-3	Cl	H	Cl	H	—	
A-4	F	H	H	H	—	
A-5	H	H	F	H	—	
A-6	Br	H	H	H	—	

TABLE 9-continued



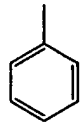
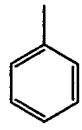
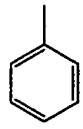
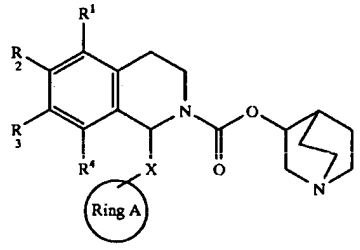
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-7	H	H	Br	H	—	
A-8	Cl	H	Br	H	—	
A-9	CH_3	H	H	H	—	

TABLE 10



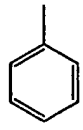
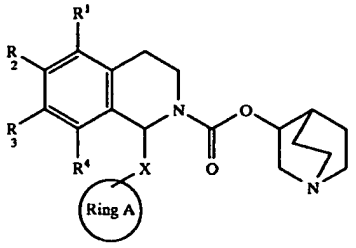
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-10	C_2H_5	H	H	H	—	

TABLE 10-continued



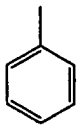
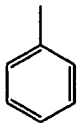
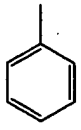
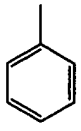
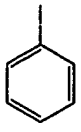
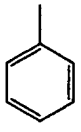
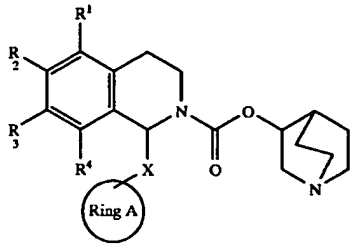
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-11	n-C_3H_7	H	H	H	—	 —
A-12	i-C_3H_7	H	H	H	—	 —
A-13	H	CH_3	H	H	—	 —
A-14	H	C_2H_5	H	H	—	 —
A-15	H	H	CH_3	H	—	 —
A-16	H	R	C_2H_5	H	—	 —

TABLE 10-continued



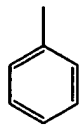
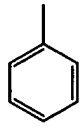
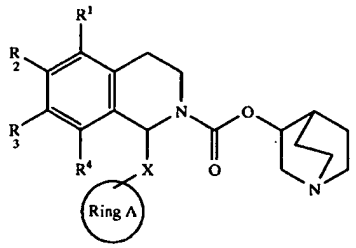
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-17	CH_3	H	CH_3	H	—	 —
A-18	H	CH_3	CH_3	H	—	 —

TABLE 11



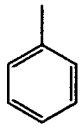
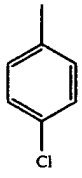
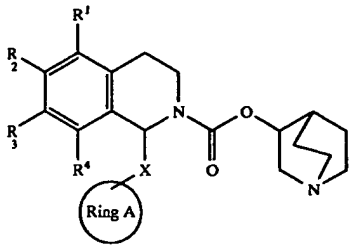
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-19	CH_3	H	CH_3	CH_3	—	 —
A-20	Cl	H	H	H	—	 Cl —

TABLE 11-continued



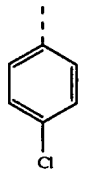
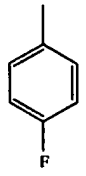
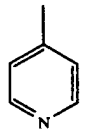
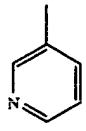
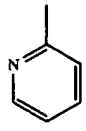
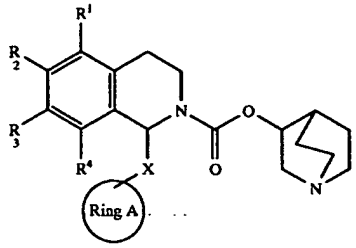
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-21	H	H	Cl	H	—	 —
A-22	H	H	Cl	H	—	 —
A-23	H	H	Cl	H	—	 —
A-24	H	H	Cl	H	—	 —
A-25	H	H	Cl	H	—	 —

TABLE 12



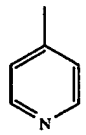
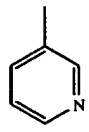
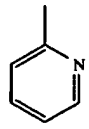
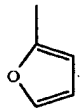
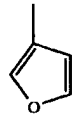
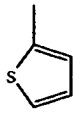
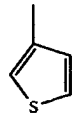
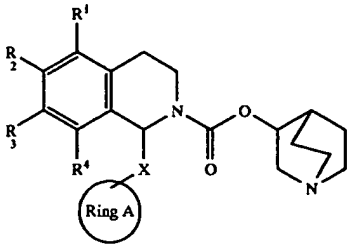
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-26	H	H	CH_3	H	—	 —
A-27	Cl	H	H	H	—	 —
A-28	H	CH_3	H	H	—	 —
A-29	Cl	H	H	H	—	 —
A-30	Cl	H	H	H	—	 —
A-31	H	H	Cl	H	—	 —
A-32	H	H	Cl	H	—	 —

TABLE 12-continued



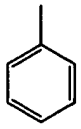
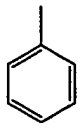
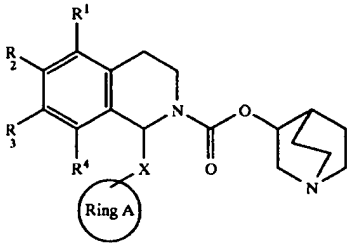
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-33	H	OCH_3	OCH_3	H	—	
A-34	H	$—OCH_2O—$		H	—	

TABLE 13



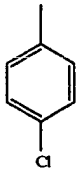
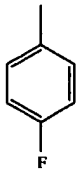
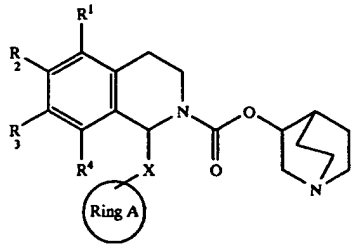
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-35	H	H	H	H	CH_2	
A-36	H	H	H	H	CH_2	

TABLE 13-continued



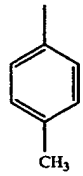
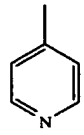
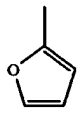
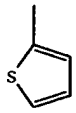
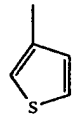
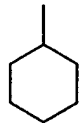
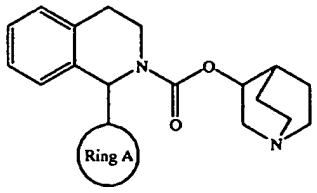
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-37	H	H	H	H	CH_2	
A-38	H	H	H	H	CH_2	
A-39	H	H	H	H	CH_2	
A-40	Cl	H	H	H	CH_2	
A-41	Cl	H	H	H	CH_2	
A-42	Cl	H	H	H	CH_2	

TABLE 14



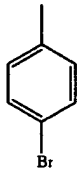
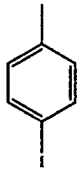
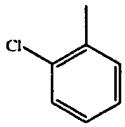
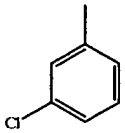
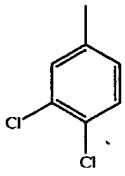
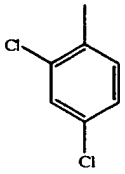
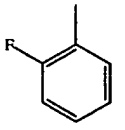
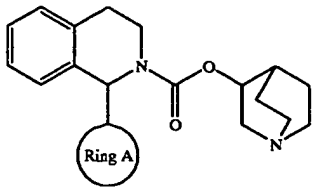
Compound No.	Ring A
B-1	
B-2	
B-3	
B-4	
B-5	
B-6	
B-7	

TABLE 14-continued



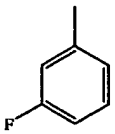
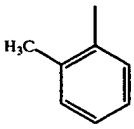
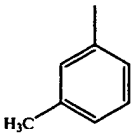
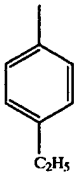
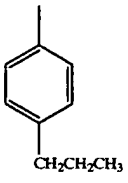
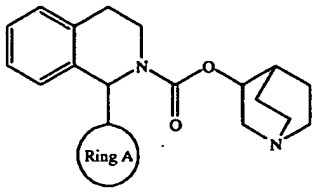
Compound No.	Ring A
B-8	
B-9	
B-10	
B-11	
B-12	

TABLE 15



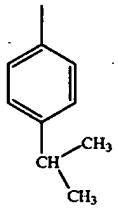
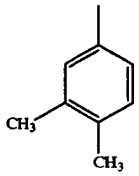
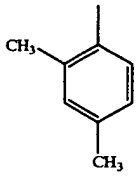
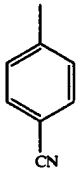
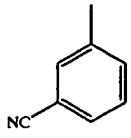
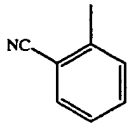
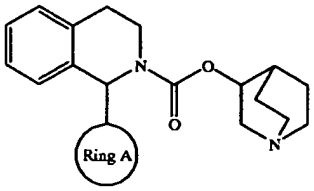
Compound No.	Ring A
B-13	
B-14	
B-15	
B-16	
B-17	
B-18	

TABLE 15-continued



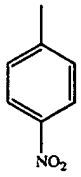
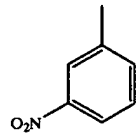
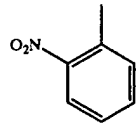
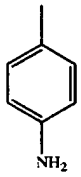
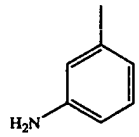
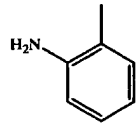
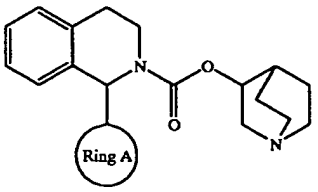
Compound No.	Ring A
B-19	
B-20	
B-21	
B-22	
B-23	
B-24	

TABLE 16



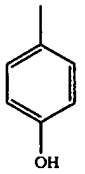
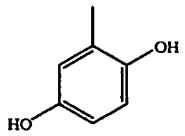
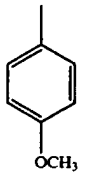
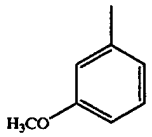
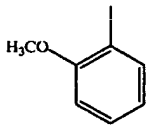
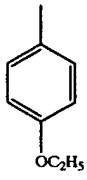
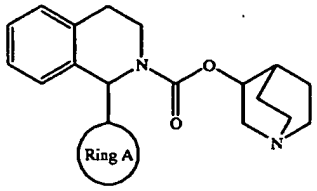
Compound No.	Ring A
B-25	
B-26	
B-27	
B-28	
B-29	
B-30	

TABLE 16-continued



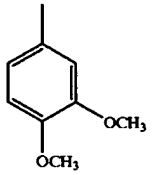
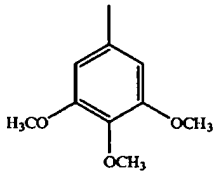
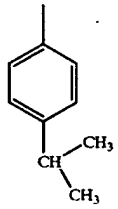
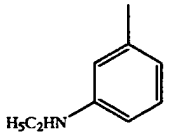
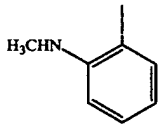
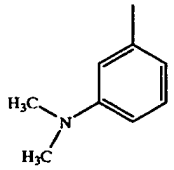
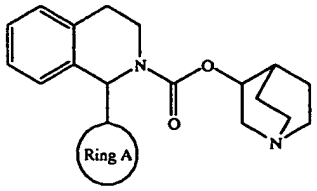
Compound No.	Ring A
B-31	
B-32	
B-33	
B-34	
B-35	
B-36	

TABLE 17



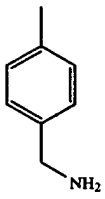
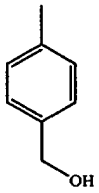
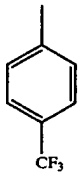
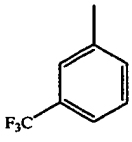
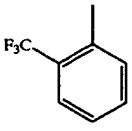
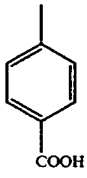
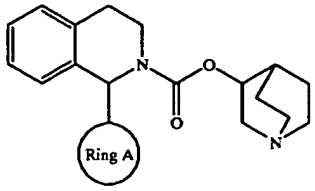
Compound No.	Ring A
B-37	
B-38	
B-39	
B-40	
B-41	
B-42	

TABLE 17-continued



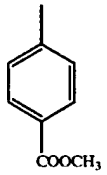
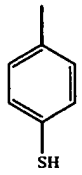
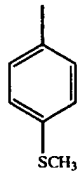
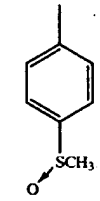
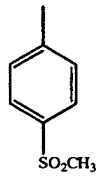
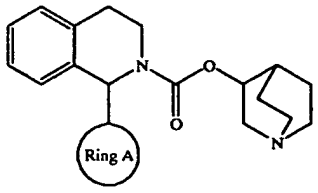
Compound No.	Ring A
B-43	
B-44	
B-45	
B-46	
B-47	
B-48	

TABLE 18



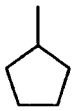
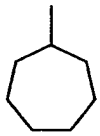
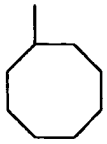
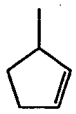
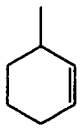
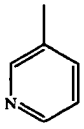
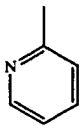
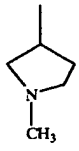
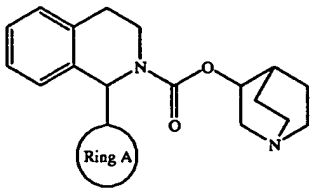
Compound No.	Ring A
B-49	
B-50	
B-51	
B-52	
B-53	
B-54	
B-55	
B-56	

TABLE 18-continued



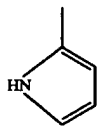
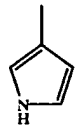
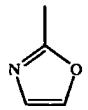
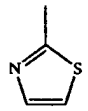
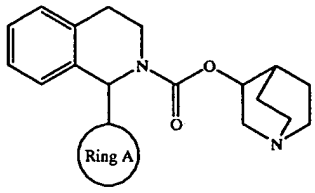
Compound No.	Ring A
B-57	
B-58	
B-59	
B-60	

TABLE 19



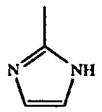
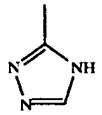
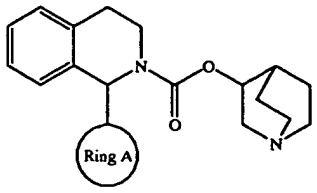
Compound No.	Ring A
B-61	
B-62	

TABLE 19-continued



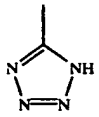
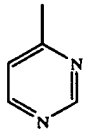
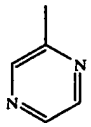
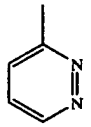
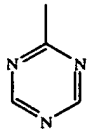
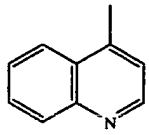
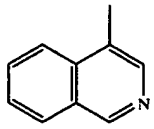
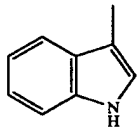
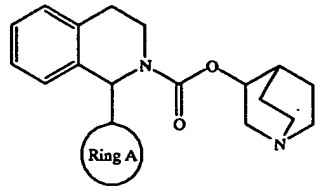
Compound No.	Ring A
B-63	
B-64	
B-65	
B-66	
B-67	
B-68	
B-69	
B-70	

TABLE 19-continued



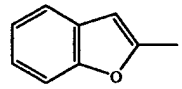
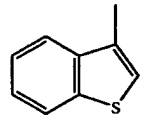
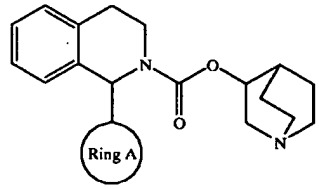
Compound No.	Ring A
B-71	
B-72	

TABLE 20



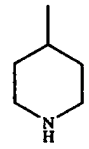
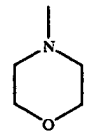
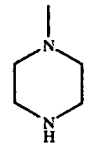
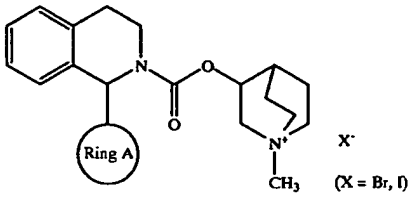
Compound No.	Ring A
B-73	
B-74	
B-75	

TABLE 21



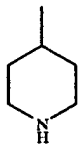
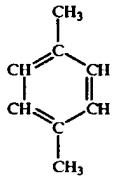
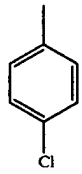
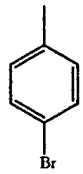
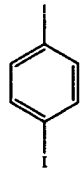
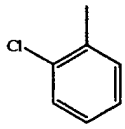
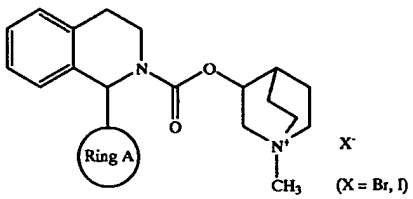
Compound No.	Ring A
B-76	
B-77	
B-78	
B-79	
B-80	
B-81	

TABLE 21-continued



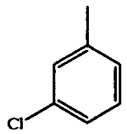
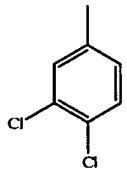
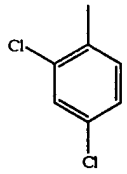
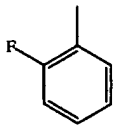
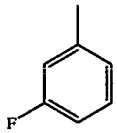
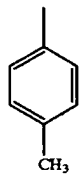
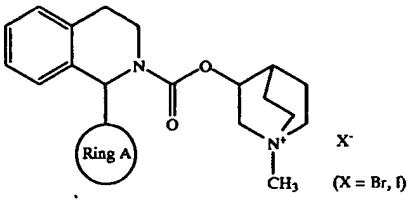
Compound No.	Ring A
B-82	
B-83	
B-84	
B-85	
B-86	
B-87	

TABLE 22



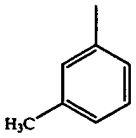
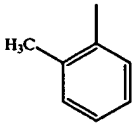
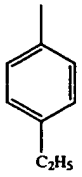
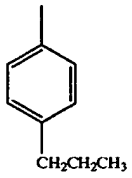
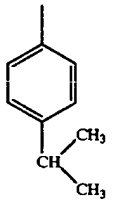
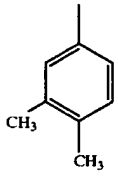
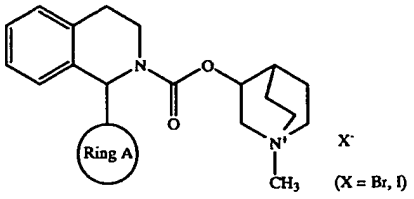
Compound No.	Ring A
B-88	
B-89	
B-90	
B-91	
B-92	
B-93	

TABLE 22-continued



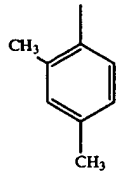
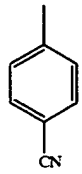
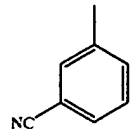
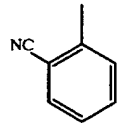
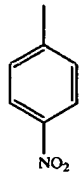
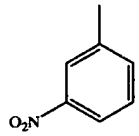
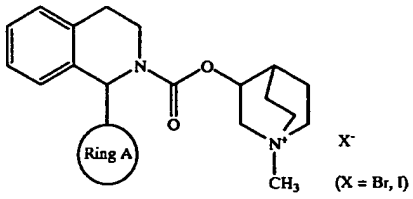
Compound No.	Ring A
B-94	
B-95	
B-96	
B-97	
B-98	
B-99	

TABLE 23



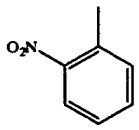
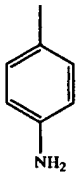
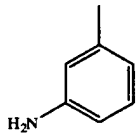
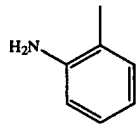
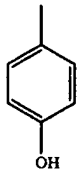
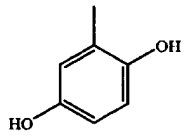
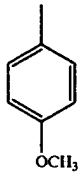
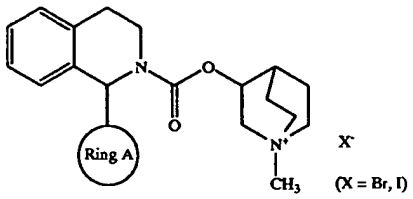
Compound No.	Ring A
B-100	
B-101	
B-102	
B-103	
B-104	
B-105	
B-106	

TABLE 23-continued



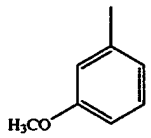
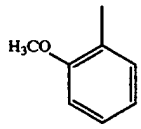
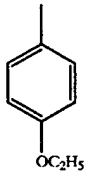
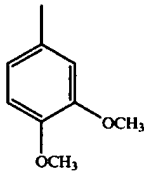
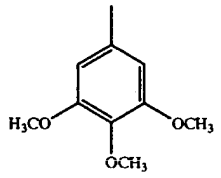
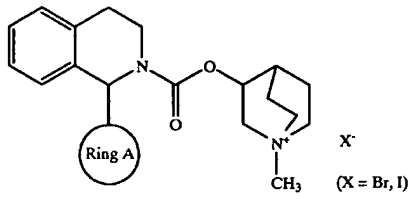
Compound No.	Ring A
B-107	
B-108	
B-109	
B-110	
B-111	

TABLE 24



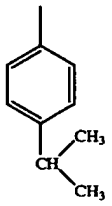
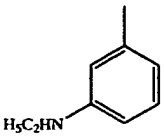
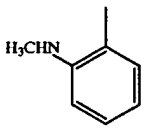
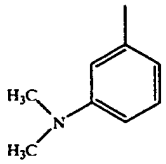
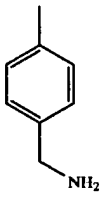
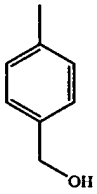
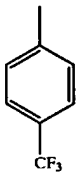
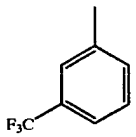
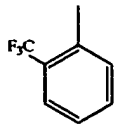
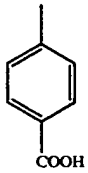
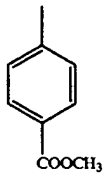
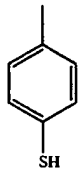
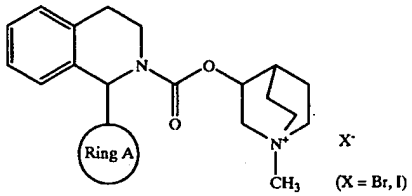
Compound No.	Ring A
B-112	
B-113	
B-114	
B-115	
B-116	
B-117	
B-118	
B-119	
B-120	
B-121	
B-122	
B-123	

TABLE 25



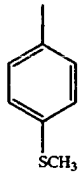
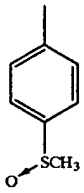
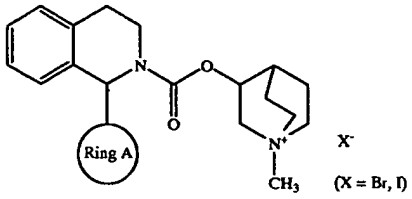
Compound No.	Ring A
B-124	
B-125	

TABLE 25-continued



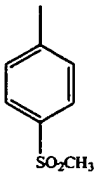
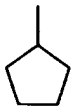
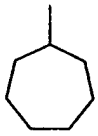
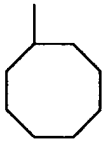
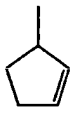
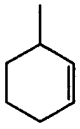
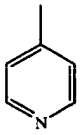
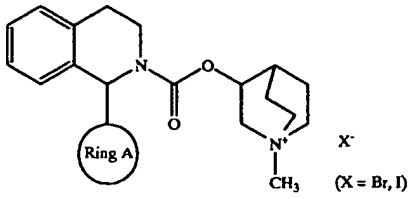
Compound No.	Ring A
B-126	
B-127	
B-128	
B-129	
B-130	
B-131	
B-132	
B-133	

TABLE 25-continued



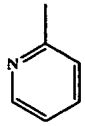
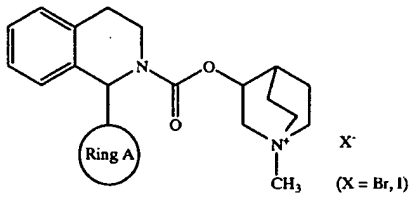
Compound No.	Ring A
B-134	
B-135	

TABLE 26



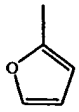
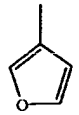
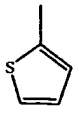
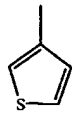
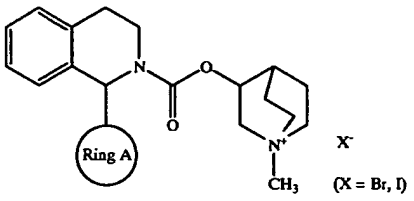
Compound No.	Ring A
B-136	
B-137	
B-138	
B-139	

TABLE 26-continued



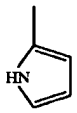
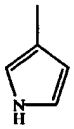
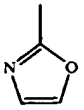
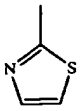
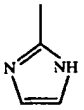
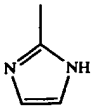
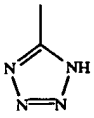
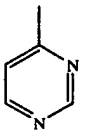
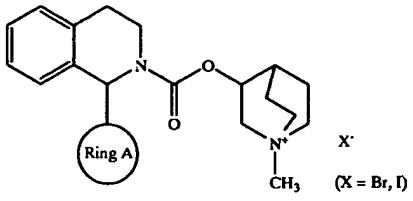
Compound No.	Ring A
B-140	
B-141	
B-142	
B-143	
B-144	
B-145	
B-146	
B-147	

TABLE 27



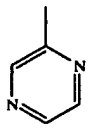
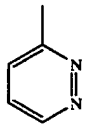
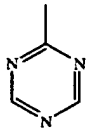
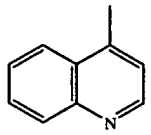
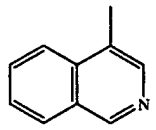
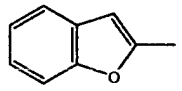
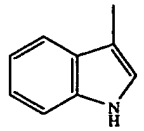
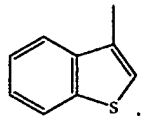
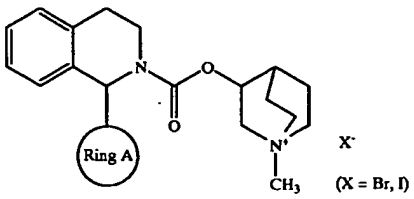
Compound No.	Ring A
B-148	
B-149	
B-150	
B-151	
B-152	
B-153	
B-154	
B-155	

TABLE 27-continued



(X = Br, I)

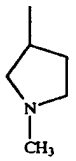
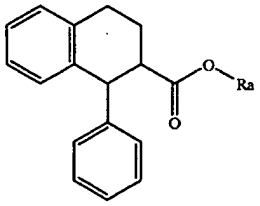
Compound No.	Ring A
B-156	

TABLE 28



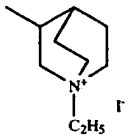
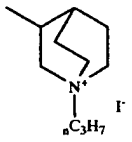
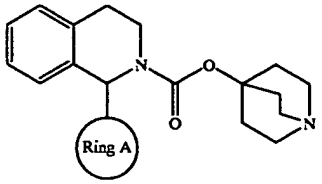
Compound No.	Ring A
B-157	
B-158	

TABLE 29



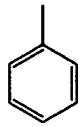
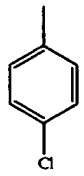
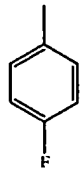
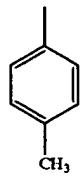
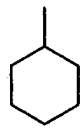
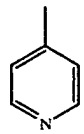
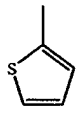
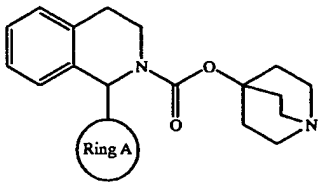
Compound No.	Ring A
B-159	
B-160	
B-161	
B-162	
B-163	
B-164	
B-165	

TABLE 29-continued



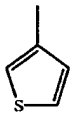
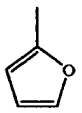
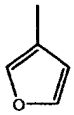
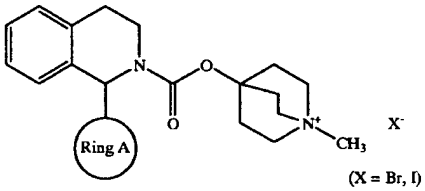
Compound No.	Ring A
B-166	
B-167	
B-168	

TABLE 30



(X = Br, I)

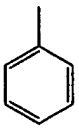
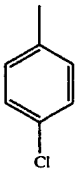
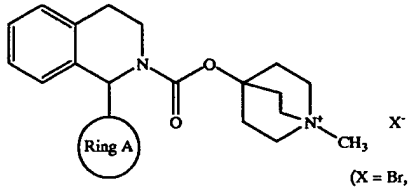
Compound No.	Ring A
B-169	
B-170	

TABLE 30-continued



(X = Br, I)

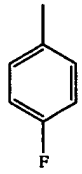
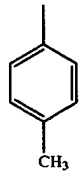
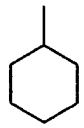
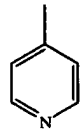
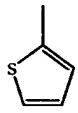
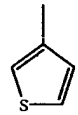
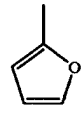
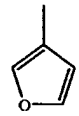
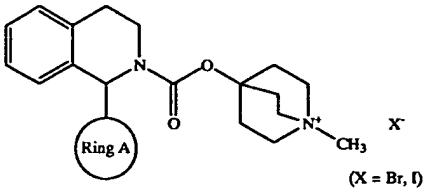
Compound No.	Ring A
B-171	
B-172	
B-173	
B-174	
B-175	
B-176	
B-177	
B-178	

TABLE 30-continued



(X = Br, I)

Compound No.	Ring A

TABLE 31

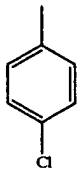
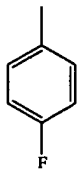
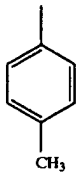
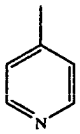
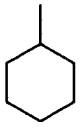
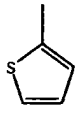
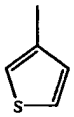
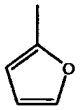
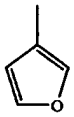
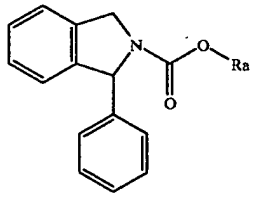
Compound No.	Ring A
B-179	
B-180	
B-181	
B-182	
B-183	
B-184	
B-185	
B-186	
B-187	

TABLE 32



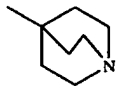
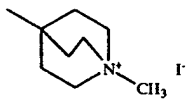
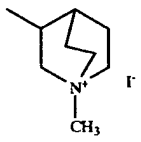
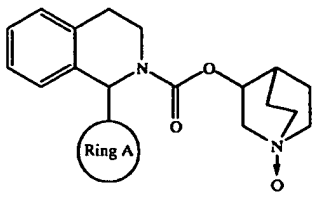
Compound No.	R_a
B-188	
B-189	
B-190	

TABLE 33



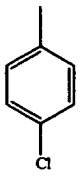
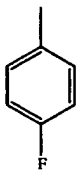
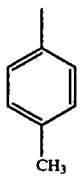
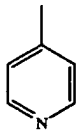
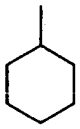
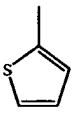
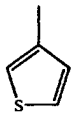
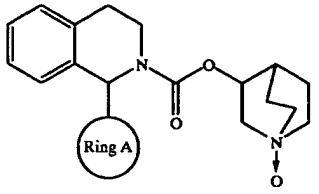
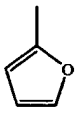
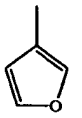
Compond No.	Ring A
B-191	
B-192	
B-193	
B-194	
B-195	
B-196	
B-197	

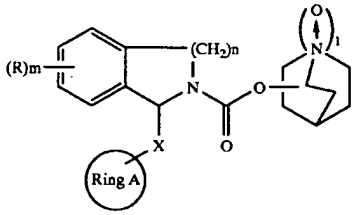
TABLE 33-continued



Compond No.	Ring A
B-198	
B-199	

We claim:

1. A quinuclidine derivative represented by the following formula (I):



(I)

where the symbols in the formula have the following meanings:

Ring A:

(1) an aryl group having 6 to 14 carbon atoms

(3) a cycloalkyl group having 3 to 8 carbon atoms

(4) a cycloalrenye group having 3to 8 carbon atoms;

wherein groups (1) to (5) above may be unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower aklylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group, and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxyl group, an amino group or mono- or di-lower alkylamino group

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower akylsulfonyl group, a sulfinyl group, a lower alkylsufinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1;

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2,

a salt thereof, an N-oxide thereof, or a quaternary ammonium salt thereof.

2. The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to claim 1, wherein R represents a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and the ring A represents an aryl group having 6 to 14 carbon atoms, a cycloalkyl group having 3 to 8 carbon atoms or a cycloalkenyl group having 3 to 8 carbon atoms, in which said ring may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxyl group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group.

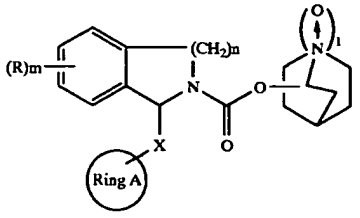
3. The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to claim 2, wherein m is 0, and the ring A represents an aryl group, a cycloalkyl group or a cycloalkenyl group which may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group or a lower alkoxy group.

4. The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to claim 3, wherein the ring A represents a phenyl group which may be substituted by a halogen atom or a lower alkyl group, or cycloalkyl group.

5. The quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to any one of claims 2 to 4, wherein X represents a single bond.

6. A quinuclidine derivative, a salt thereof, or a quaternary ammonium salt thereof according to any one of claim 1, which is selected from the group consisting of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate, and 3-quinuclidinyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate.

7. A pharmaceutical composition which comprises a quinuclidine derivative represented by the following formula (I):



where the symbols in the formula have the following meanings:

Ring A:

(1) an aryl group having 6 to 14 carbon atoms

(3) a cycloalkyl group having 3 to 8 carbon atoms

(4) a cycloakenyl group having 3 to 8 carbon atoms;

wherein groups (1) to (5) above may be unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxul group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower aklylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxyl group, an amino group or mono- or di-lower alkylamino group

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower akylsulfonyl group, a sulfinyl group, a lower alkylsufinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1;

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2, or

a salt thereof, an N-oxide thereof, or a quaternary ammonium salt thereof,

and a pharmaceutically acceptable carrier.

* * * * *

ATTACHMENT 3A

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 14,
Lines 22 and 25, delete "(1R)" and insert -- (1S) --;
Lines 35 and 53, delete "C" and insert -- c -- (i.e. small letter); and
Lines 41 and 43, delete "(1S)" and insert -- (1R) --.

Column 21,
Lines 14 and 44, delete "(1R)" and insert -- (1S) --;
Line 31, delete "(1R,3'RS)" and insert -- (1S,3'RS) --; and
Line 63, delete "(1R,3'R)" and insert -- (1S,3'R) --.

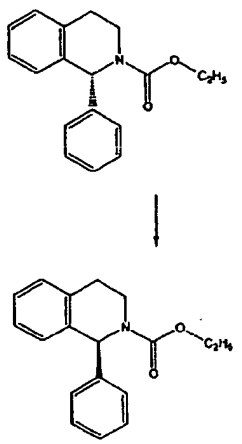
Column 22,
Line 16, delete "(1S,3'S)" and insert -- (1R,3'S) --;
Lines 19 and 37, delete "(1S)" and insert -- (1R) --;
Line 34, delete "(1S,3'R)" and insert -- (1R,3'R) --;
Line 53, delete "(1R,3'S)" and insert -- (1S,3'S) --; and
Line 56, delete "(1R)" and insert -- (1S) --.

Column 24,
Line 19, delete "(1R,3'R)" and insert -- (1S, 3'R) --;
Lines 31 and 50, delete "(1'R,3R)" and insert -- (1'S,3R) --; and
Line 44, delete "(1R,3'R)" and insert -- (1S,3'R) --.

Columns 33 to 40,
Tables 9 to 13, "R_2" and "R_3" should be changed to -- R^2 -- and -- R^3 --.

Column 16,
Table 1, Example No. 7, the chemical formula should be changed as follows:

Table 1
Example 7



UNITED STATES PATENT AND TRADEMARK OFFICE

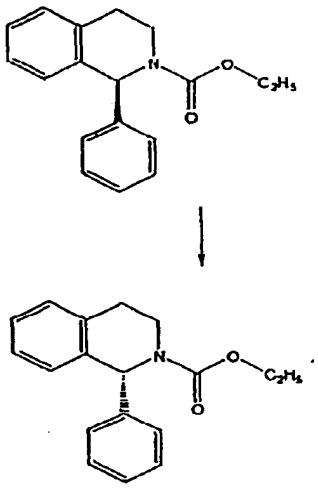
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927 Page 2 of 16
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

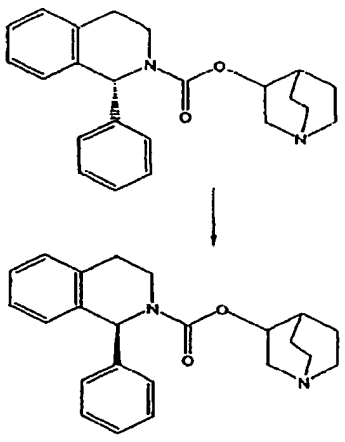
Column 17,
Table 1, Example No. 8, the chemical formula should be changed as follows:

Table 1
Example 8



Column 26,
Table 3, Example No. 7, the chemical formula should be changed as follows:

Table 3
Example 7



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26 (cont'd),

Table 3, Example No. 8, the chemical formula should be changed as follows:

Table 3
Example 8

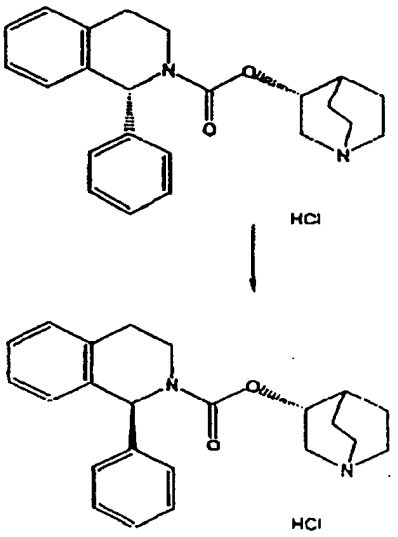
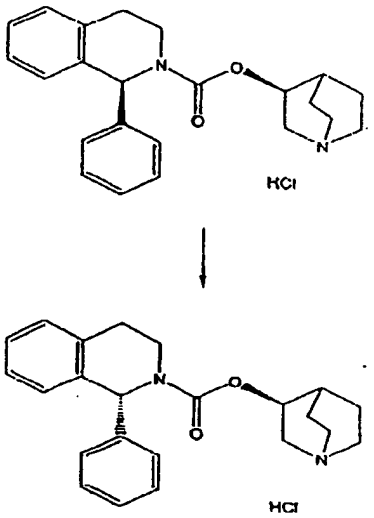


Table 3, Example No. 9, the chemical formula should be changed as follows:

Table 3
Example 9



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

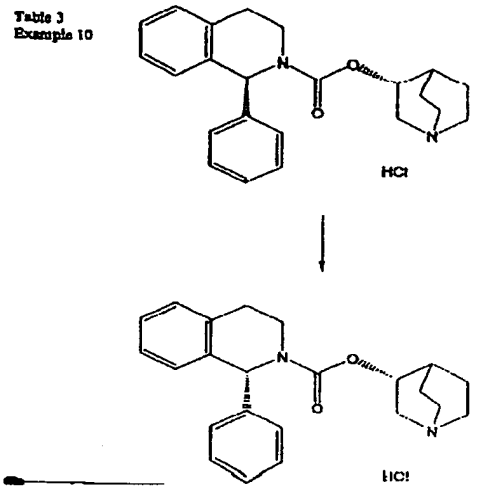
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26 (cont'd),

Table 3, Example No. 10, the chemical formula should be changed as follows:

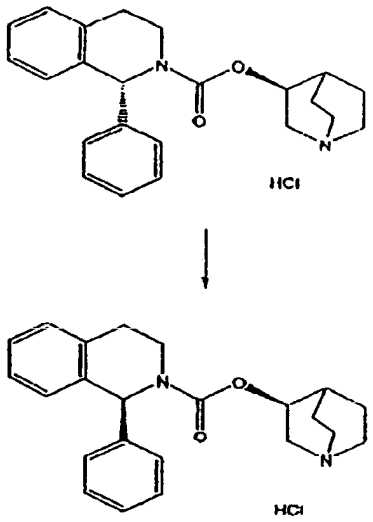
Table 3
Example 10



Column 27,

Table 4, Example No. 11, the chemical formula should be changed as follows:

Table 4
Example 11



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,

Table 4, Example No.17, the chemical formula should be changed as follows:

Table 4
Example 17

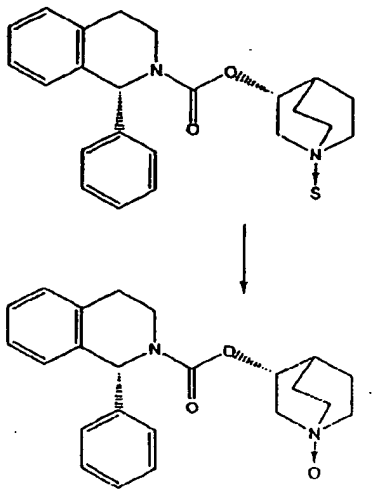
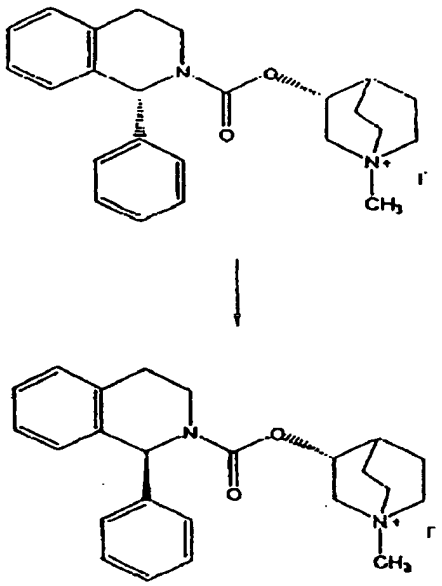


Table 4, Example No. 18, the chemical formula should be changed as follows:

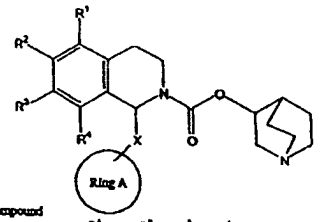
Table 4
Example 18



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39,
Delete Tables 9 to 12, and replace with the following:

TABLE 9



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-1	Cl	H	H	H	—	
A-2	H	H	Cl	H	—	
A-3	Cl	H	Cl	H	—	
A-4	F	H	H	H	—	
A-5	H	H	F	H	—	
A-6	Br	H	H	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

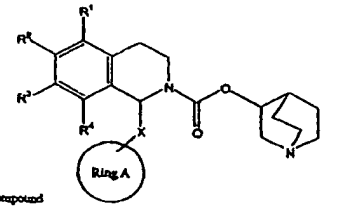
CERTIFICATE OF CORRECTION

DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 9-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-7	H	H	Br	H	—	
A-8	Cl	H	Br	H	—	
A-9	CH_3	H	H	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

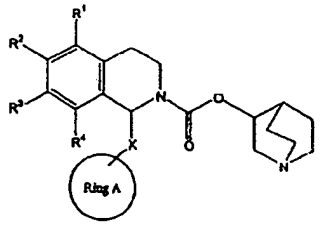
CERTIFICATE OF CORRECTION

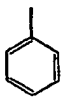
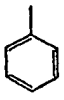
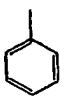
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 10

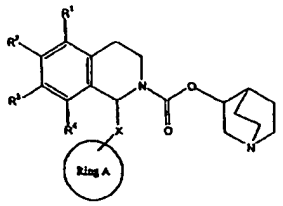


Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-10	C_2H_5	H	H	H	—	
A-11	n-C_3H_7	H	H	H	—	
A-12	i-C_3H_7	H	H	H	—	
A-13	H	CH_3	H	H	—	
A-14	H	C_2H_5	H	H	—	

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 10-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-15	H	H	CH_3	H	—	
A-16	H	R	C_2H_5	H	—	
A-17	CH_3	H	CH_3	H	—	
A-18	H	CH_3	CH_3	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

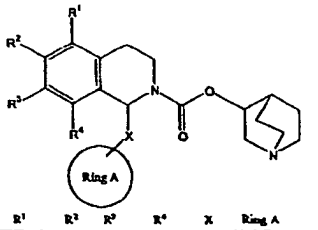
CERTIFICATE OF CORRECTION

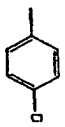
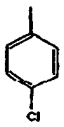
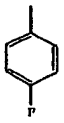
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 11



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-19	CH_3	H	CH_3	CH_3	—	
A-20	Cl	H	H	H	—	
A-21	H	H	Cl	H	—	
A-22	H	H	Cl	H	—	
A-23	H	H	Cl	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

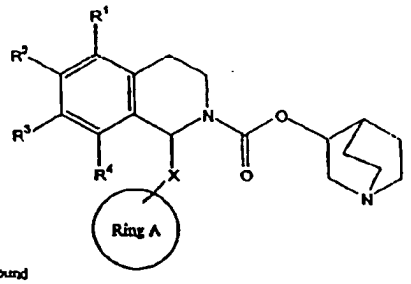
CERTIFICATE OF CORRECTION

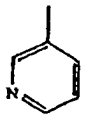
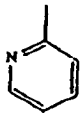
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 11-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-24	H	H	Cl	H	–	
A-25	H	H	Cl	H	–	

UNITED STATES PATENT AND TRADEMARK OFFICE

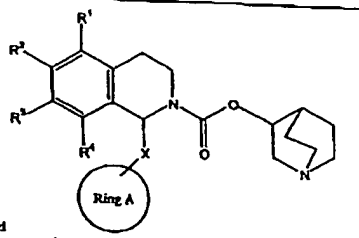
CERTIFICATE OF CORRECTION

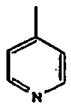
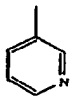
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 12

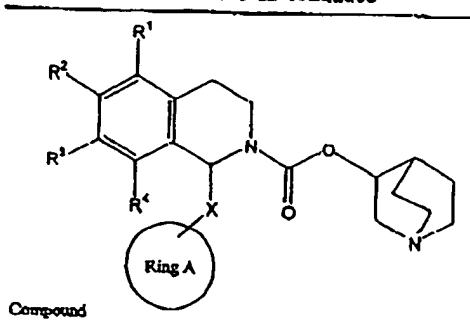


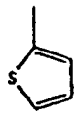
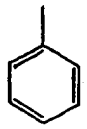
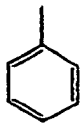
Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-26	H	H	CH_3	H	—	
A-27	Cl	H	H	H	—	
A-28	H	CH_3	H	H	—	
A-29	Cl	H	H	H	—	
A-30	Cl	H	H	H	—	

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 12-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-31	H	H	Cl	H	—	
A-32	H	H	Cl	H	—	
A-33	H	OCH_3	OCH_3	H	—	
A-34	H	$-OCH_2O-$		H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

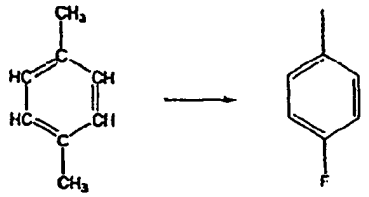
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 53,
Table 21, Column B-77, the chemical formula should be changed as follows:

Table 21
Compound B-77



Column 62,
Table 25, Compound B-134, the chemical formula should be changed as follows:

Table 25
Compound B-134

Column 63,
Table 26, Compound B-145, the chemical formula should be changed as follows:

Table 26
Compound B-145

UNITED STATES PATENT AND TRADEMARK OFFICE

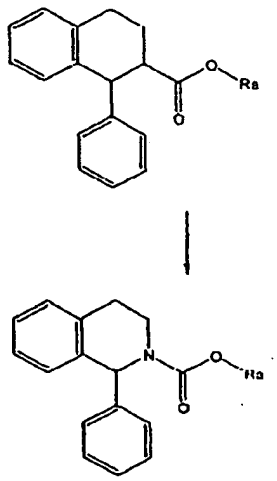
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

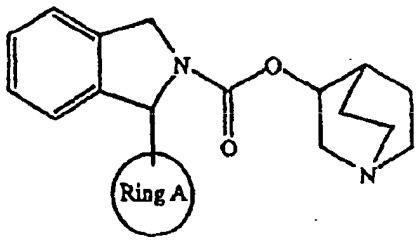
Column 65,
Table 28, the chemical formula should be changed as follows:

Table 28



Column 69,
Table 31, the following chemical formula is missing:

Table 31



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Masamitsu Tsukamoto et al.

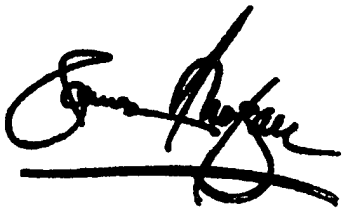
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 72,
Line 22, "cycloakenyl" should be corrected to -- cycloalkenyl --;
Line 45, "akylsulfonyl" should be corrected to -- alkylsulfonyl --;
Line 49, "cycloalrenye" should be corrected to -- cycloalkenyl --.

Column 74,
Line 22, "cycloakenyl" should be corrected to -- cycloalkenyl --;
Line 45, "akylsulfonyl" should be corrected to -- alkylsulfonyl --.

Signed and Sealed this

Twenty-fifth Day of February, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

ATTACHMENT 3B

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 14,
Lines 22 and 25, delete "(1R)" and insert -- (1S) --;
Lines 35 and 53, delete "C" and insert -- c -- (i.e. small letter); and
Lines 41 and 43, delete "(1S)" and insert -- (1R) --.

Column 21,
Lines 14 and 44, delete "(1R)" and insert -- (1S) --;
Line 31, delete "(1R,3'RS)" and insert -- (1S,3'RS) --; and
Line 63, delete "(1R,3'R)" and insert -- (1S,3'R) --.

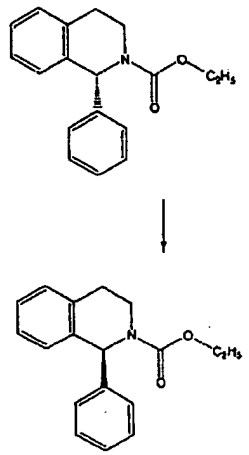
Column 22,
Line 16, delete "(1S,3'S)" and insert -- (1R,3'S) --;
Lines 19 and 37, delete "(1S)" and insert -- (1R) --;
Line 34, delete "(1S,3'R)" and insert -- (1R,3'R) --;
Line 53, delete "(1R,3'S)" and insert -- (1S,3'S) --; and
Line 56, delete "(1R)" and insert -- (1S) --.

Column 24,
Line 19, delete "(1R,3'R)" and insert -- (1S, 3'R) --;
Lines 31 and 50, delete "(1'R,3R)" and insert -- (1'S,3R) --; and
Line 44, delete "(1R,3'R)" and insert -- (1S,3'R) --.

Columns 33 to 40,
Tables 9 to 13, "R_2" and "R_3" should be changed to -- R^2 -- and -- R^3 --.

Column 16,
Table 1, Example No. 7, the chemical formula should be changed as follows:

Table 1
Example 7



UNITED STATES PATENT AND TRADEMARK OFFICE

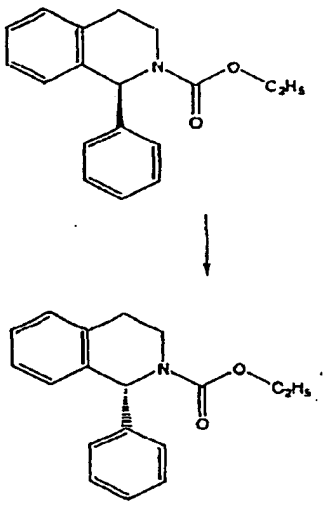
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

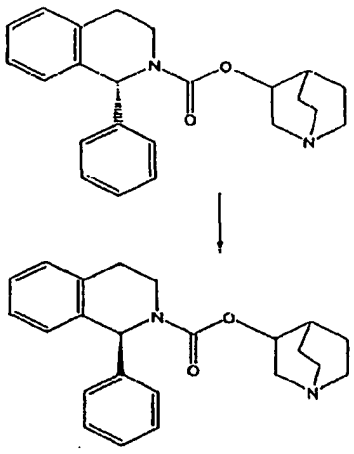
Column 17,
Table 1, Example No. 8, the chemical formula should be changed as follows:

Table 1
Example 8



Column 26,
Table 3, Example No. 7, the chemical formula should be changed as follows:

Table 3
Example 7



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927 Page 3 of 16
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26 (cont'd),

Table 3, Example No. 8, the chemical formula should be changed as follows:

Table 3
Example 8

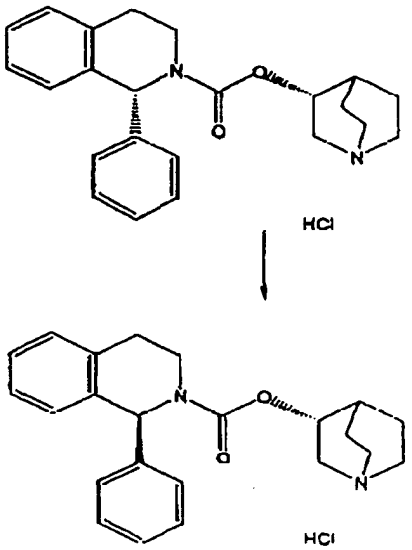
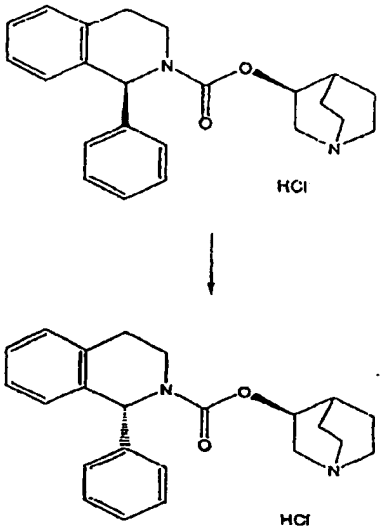


Table 3, Example No. 9, the chemical formula should be changed as follows:

Table 3
Example 9



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

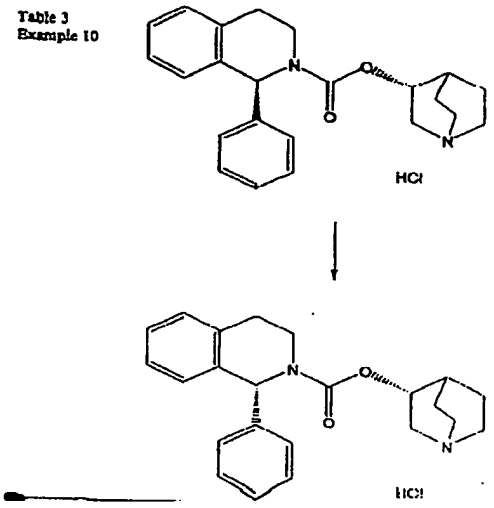
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26 (cont'd),

Table 3, Example No. 10, the chemical formula should be changed as follows:

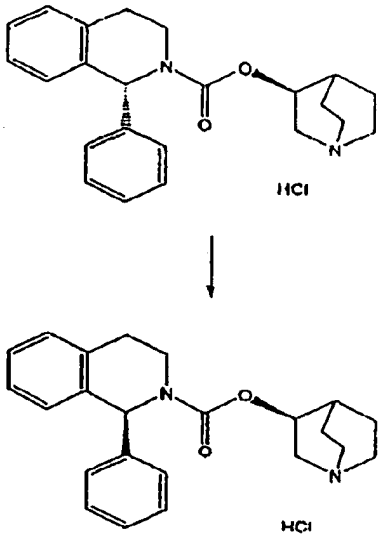
Table 3
Example 10



Column 27,

Table 4, Example No. 11, the chemical formula should be changed as follows:

Table 4
Example 11



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 28,

Table 4, Example No.17, the chemical formula should be changed as follows:

Table 4
Example 17

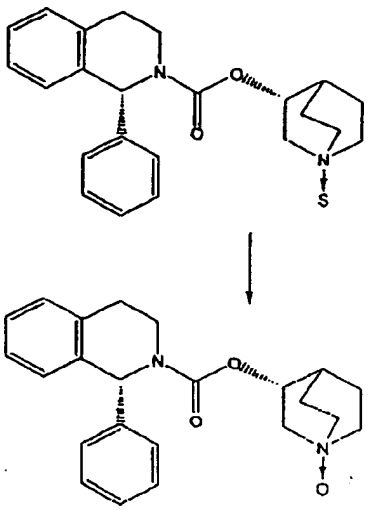
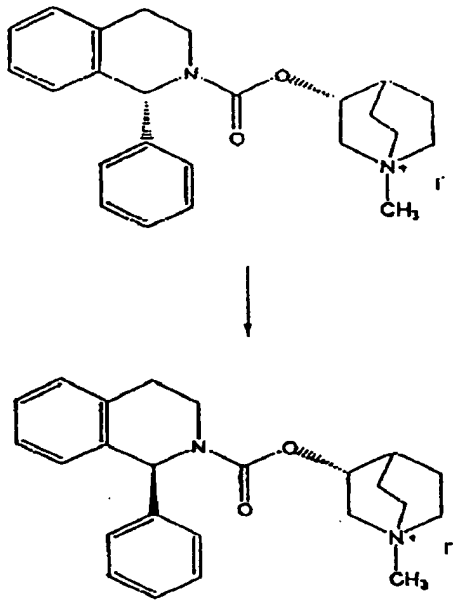


Table 4, Example No. 18, the chemical formula should be changed as follows:

Table 4
Example 18



UNITED STATES PATENT AND TRADEMARK OFFICE

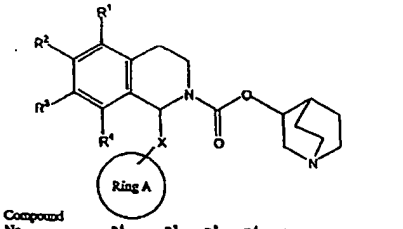
CERTIFICATE OF CORRECTION

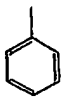
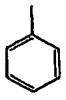
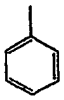
PATENT NO. : 6,017,927 Page 6 of 16
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39,
Delete Tables 9 to 12, and replace with the following:

TABLE 9



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-1	Cl	H	H	H	—	
A-2	H	H	Cl	H	—	
A-3	Cl	H	Cl	H	—	
A-4	F	H	H	H	—	
A-5	H	H	F	H	—	
A-6	Br	H	H	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

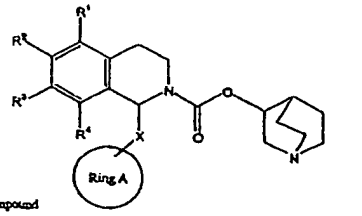
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 9-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-7	H	H	Br	H	—	
A-8	Cl	H	Br	H	—	
A-9	CH_3	H	H	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

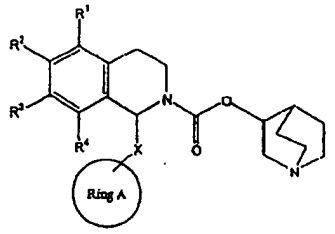
CERTIFICATE OF CORRECTION

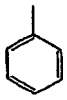
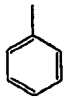
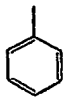
PATENT NO. : 6,017,927 Page 8 of 16
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 10



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-10	C_2H_5	H	H	H	—	
A-11	n-C_3H_7	H	H	H	—	
A-12	i-C_3H_7	H	H	H	—	
A-13	H	CH_3	H	H	—	
A-14	H	C_2H_5	H	H	—	

CERTIFICATE OF CORRECTION

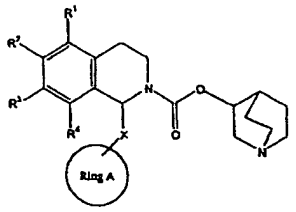
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),

Delete Tables 9 to 12, and replace with the following:

TABLE 10-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-15	H	H	CH_3	H	—	
A-16	H	H	C_2H_5	H	—	
A-17	CH_3	H	CH_3	H	—	
A-18	H	CH_3	CH_3	H	—	

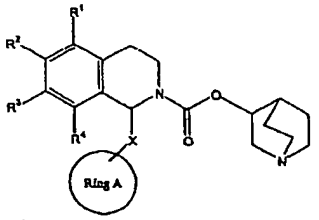
CERTIFICATE OF CORRECTION

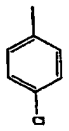
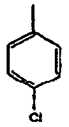
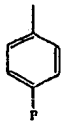
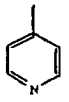
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 11



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-19	CH_3	H	CH_3	CH_3	—	
A-20	Cl	H	H	H	—	
A-21	H	H	Cl	H	—	
A-22	H	H	Cl	H	—	
A-23	H	H	Cl	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

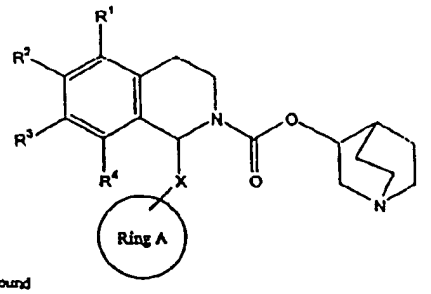
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

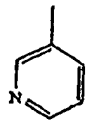
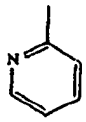
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),

Delete Tables 9 to 12, and replace with the following:

TABLE 11-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-24	H	H	Cl	H	–	
A-25	H	H	Cl	H	–	

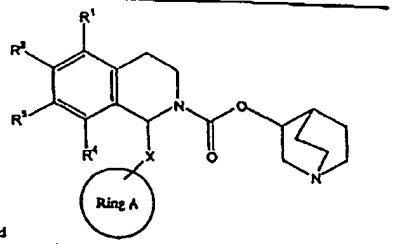
CERTIFICATE OF CORRECTION

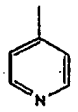
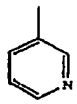
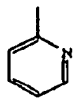
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),
Delete Tables 9 to 12, and replace with the following:

TABLE 12



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-26	H	H	CH_3	H	—	
A-27	Cl	H	H	H	—	
A-28	H	CH_3	H	H	—	
A-29	Cl	H	H	H	—	
A-30	Cl	H	H	H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

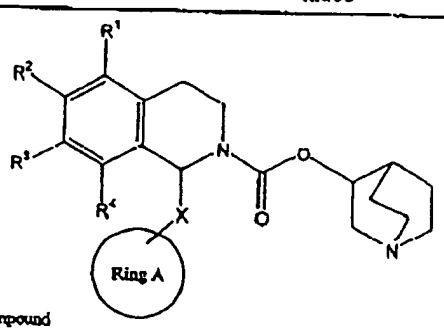
PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

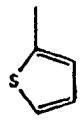
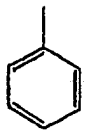
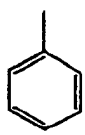
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 33 to 39 (cont'd),

Delete Tables 9 to 12, and replace with the following:

TABLE 12-continued



Compound No.	R^1	R^2	R^3	R^4	X	Ring A
A-31	H	H	Cl	H	—	
A-32	H	H	Cl	H	—	
A-33	H	OCH_3	OCH_3	H	—	
A-34	H	$-OCH_2O-$		H	—	

UNITED STATES PATENT AND TRADEMARK OFFICE

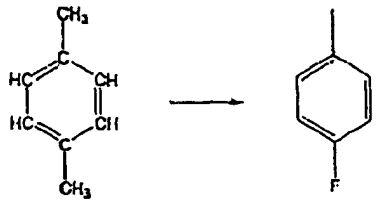
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 53,
Table 21, Column B-77, the chemical formula should be changed as follows:

Table 21
Compound B-77



Column 62,
Table 25, Compound B-134, the chemical formula should be changed as follows:

Table 25
Compound B-134

Column 63,
Table 26, Compound B-145, the chemical formula should be changed as follows:

Table 26
Compound B-145

UNITED STATES PATENT AND TRADEMARK OFFICE

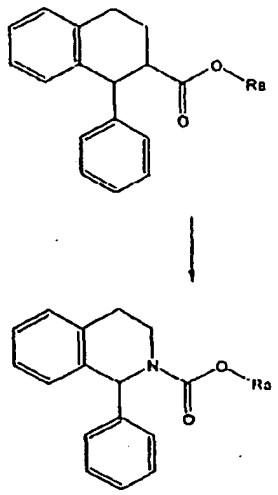
CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

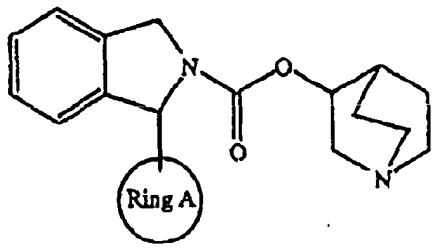
Column 65,
Table 28, the chemical formula should be changed as follows:

Table 28



Column 69,
Table 31, the following chemical formula is missing:

Table 31



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,017,927
DATED : January 25, 2000
INVENTOR(S) : Makoto Takeuchi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

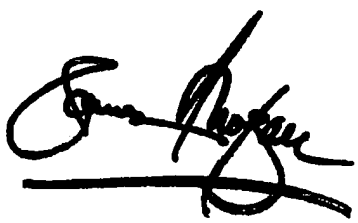
Column 72,
Line 22, "cycloakenyl" should be corrected to -- cycloalkenyl --;
Line 45, "akylsulfonyl" should be corrected to -- alkylsulfonyl --;
Line 49, "cycloalrenye" should be corrected to -- cycloalkenyl --.

Column 74,
Line 22, "cycloakenyl" should be corrected to -- cycloalkenyl --;
Line 45, "akylsulfonyl" should be corrected to -- alkylsulfonyl --.

This certificates supersedes Certificate of Correction issued February 25, 2003.

Signed and Sealed this

Seventeenth Day of June, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

ATTACHMENT 3C

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Customer No

MFFC

SUGHRUE MION ZINN MACPEAK & SEAS
2100 AVENUE NW
WASHINGTON DC 20037-3202

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	6,017,927	1551	890	0	08/860,377	01/25/00	08/28/97	04	NO	PAID

Item	Atty Dkt Number
1	Q45752

DIRECT YOUR RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
Mail Stop: M. Correspondence, Director of the United States Patent & Trademark Office
P.O. Box 1450, Alexandria, VA 22313-1450